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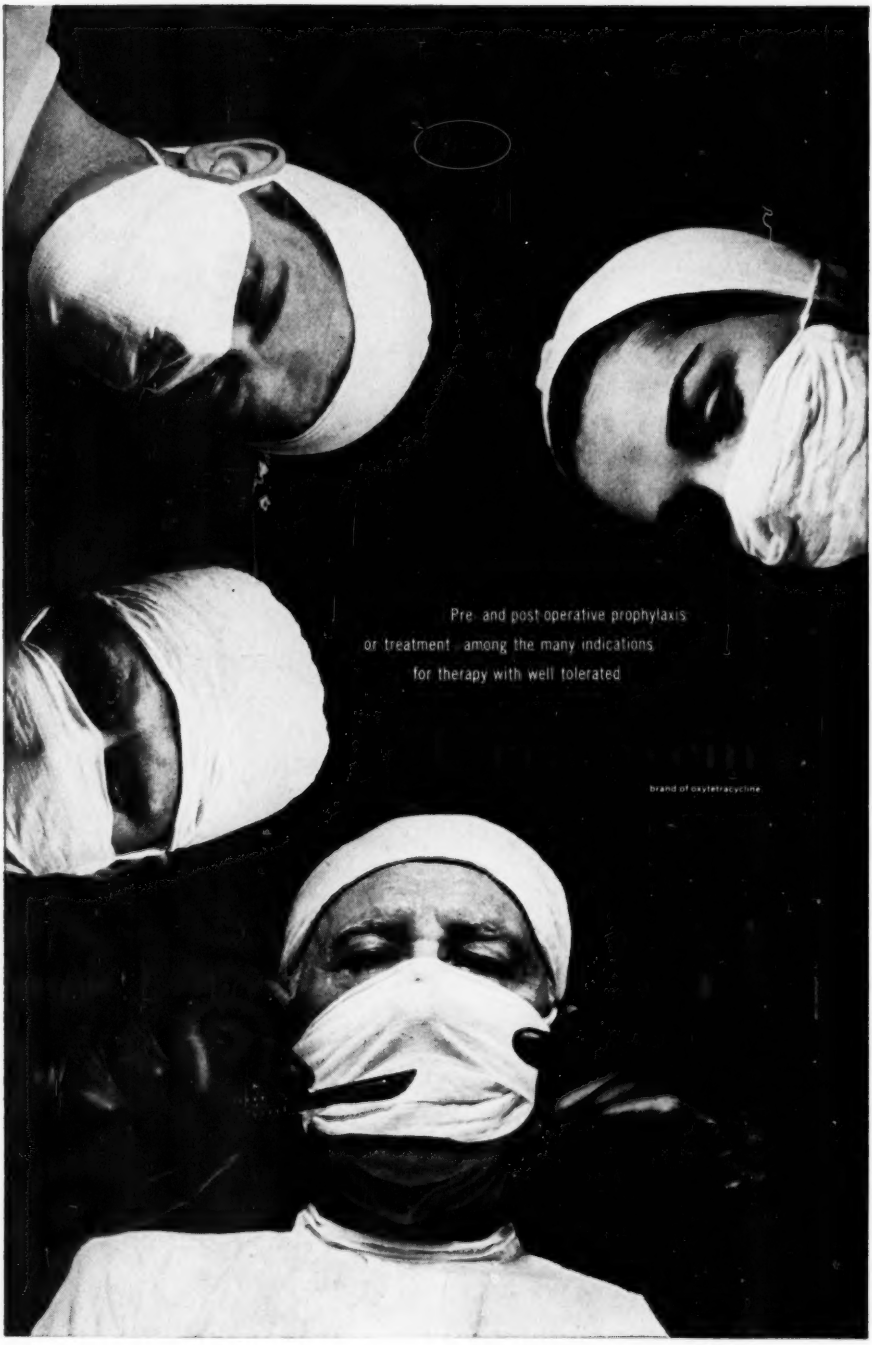
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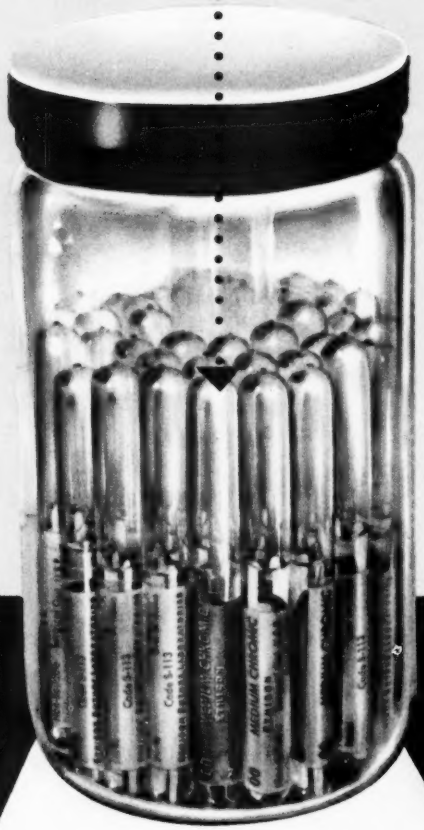

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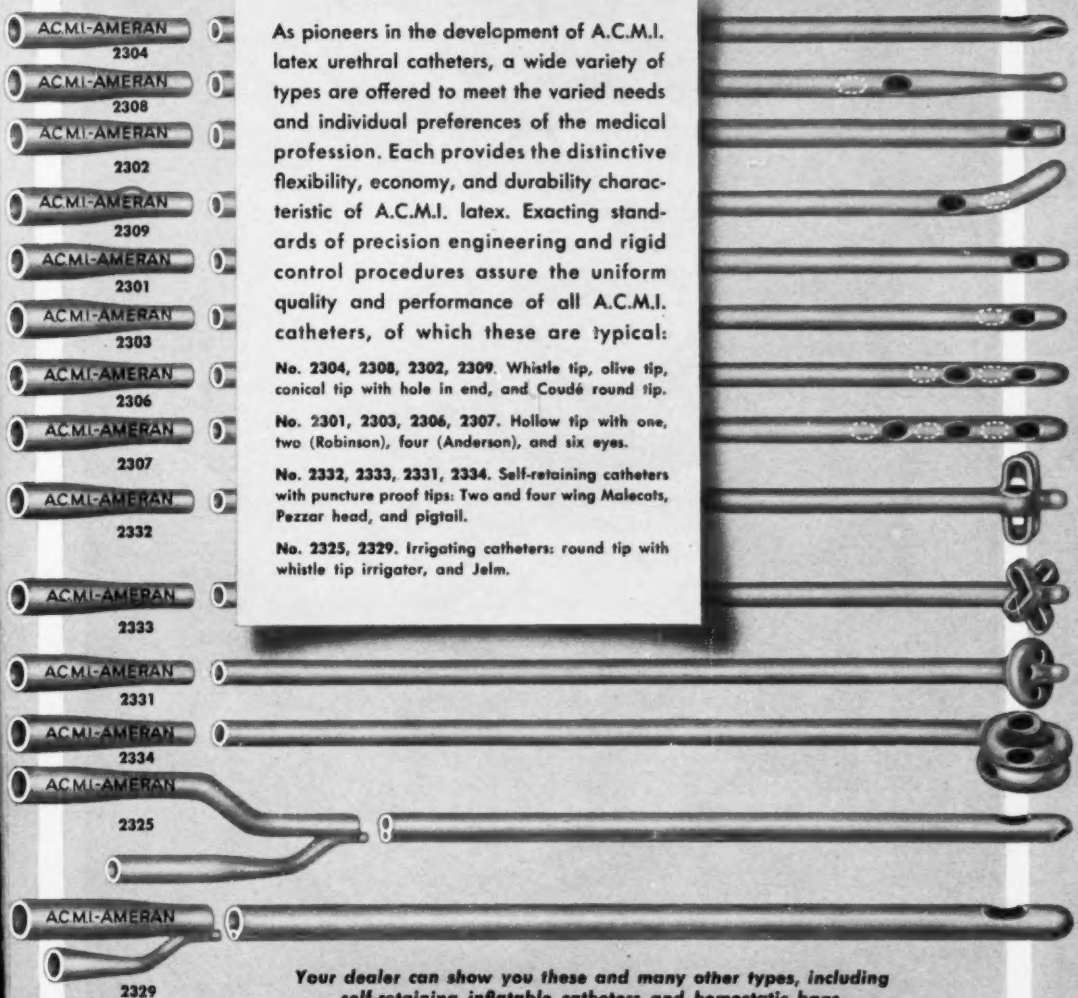

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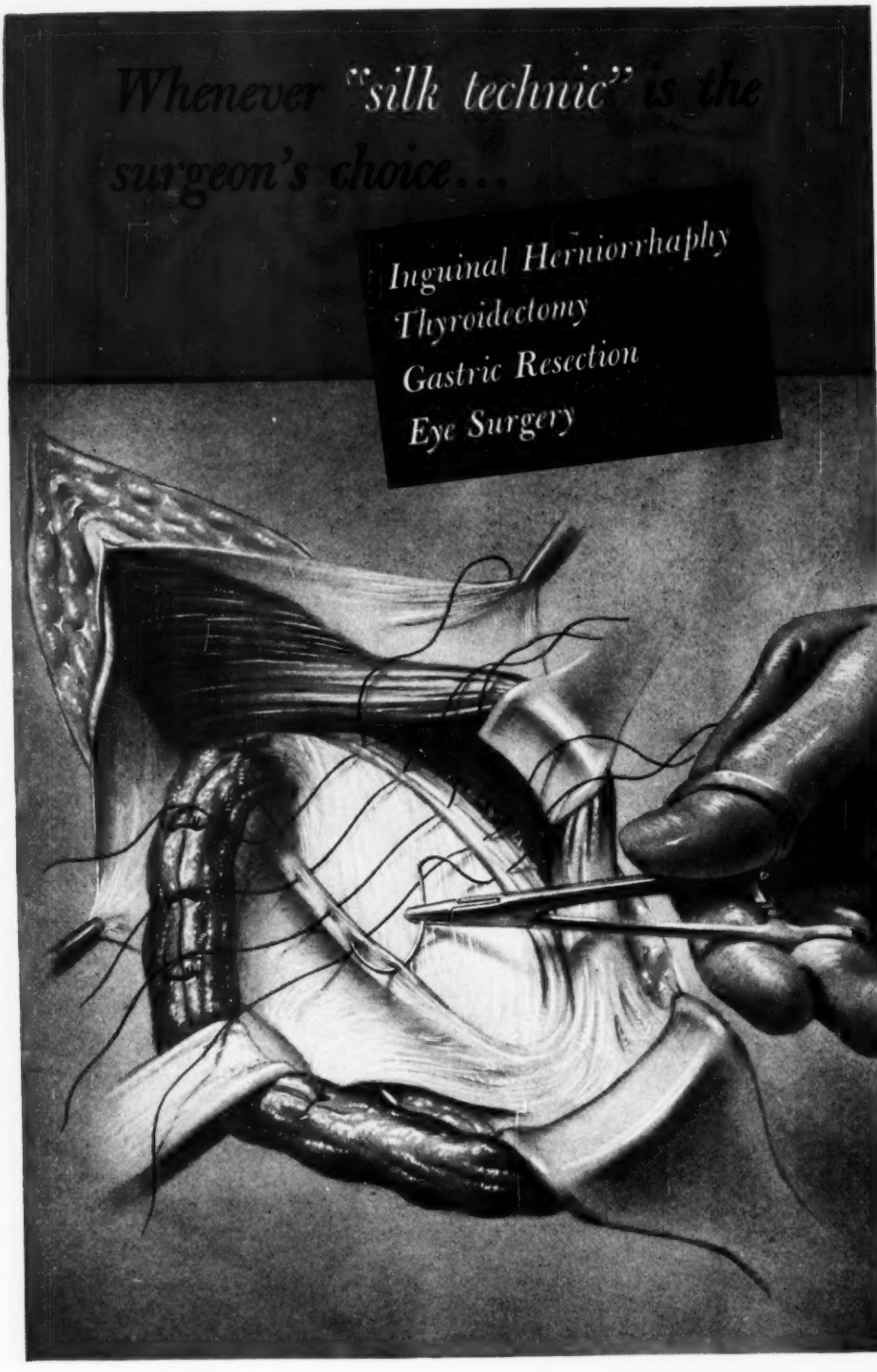
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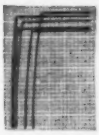

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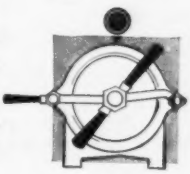

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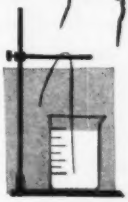

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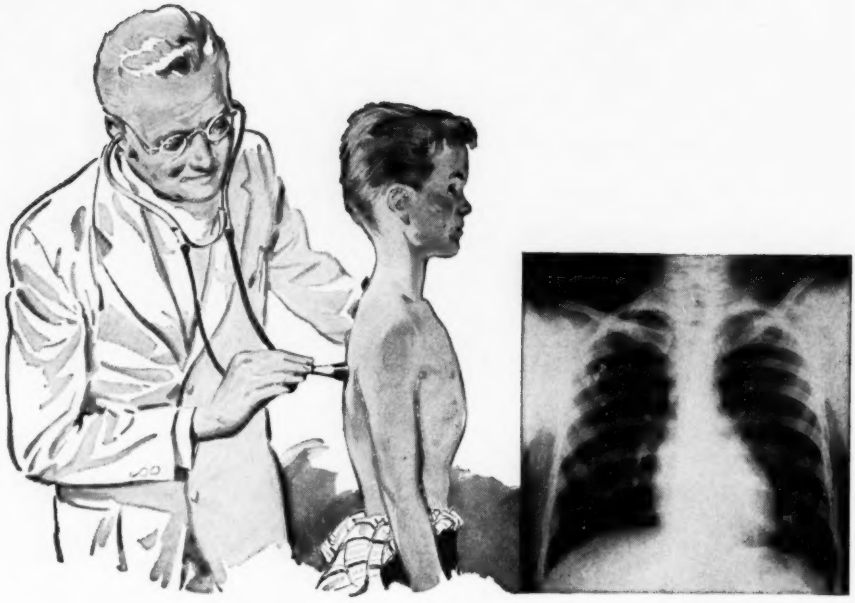

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VOLUME 66 APRIL 1953 NUMBER 4

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Editorials

SULFOBROMOPHTHALEIN APPEARANCE-TIME IN BILE

Its Diagnostic Value in Incomplete Obstructive Jaundice and in Nonicteric Obstruction of the Common Bile Duct

DETERMINATION of the sulfobromophthalein appearance-time in bile is not a laboratory procedure but a simple clinical method. Its measurement is made by the combination of duodenal intubation with the usual intravenous injection of sulfobromophthalein (150 mg. per square meter). For this purpose, the biliary fluid is simply collected by siphonage into tubes containing a few drops of 10% sodium hydroxide solution; these tubes are shaken every minute until a reddish-violet color develops. In order that the test be reliable (*a*) the output of biliary juice must be sufficient (about 1 cc. per minute as an average), and (*b*) it must contain a detectable amount of bile. Moreover, the biliary flow can be stimulated by intraduodenal instillation of procaine hydrochloride or magnesium sulfate.

In normal subjects the sulfobromophthalein appearance time ranges between 5 and 15 minutes. This test is of significant value in uncommon cases of subtotal and yet latent common bile duct obstruction. In these instances (five cases) not only is the sulfobromophthalein retained in the blood, but the appearance-time of sulfobromophthalein in bile is very delayed (from 30 to 50 minutes) despite an apparently normal biliary output. On the contrary, in cirrhosis of the liver, the sulfobromophthalein appearance-time is shortened from 5 to 8 minutes (10 cases). Unfortunately, most of the latent common bile duct calculi impair neither the biliary flow nor the sulfobromophthalein appearance-time.

The test is diagnostically the most informative in incomplete obstructive jaundice. In hepatitis with jaundice (16 cases) the sulfobromophthalein appearance-time is normal or shortened; exceptions are encountered only when a complete intrahepatic occlusion to the bile flow is present. It is the only reliable test in those cases of hepatitis with biological data of pure biliary stasis (four cases). The test also retains its value in cases of cirrhosis with jaundice (two cases).

In the course of jaundice due to incomplete common bile duct obstruction (caused by lithiasis, pancreatitis, choledocitis, postoperative stricture, carcinoma of the papilla major) despite an important biliary output, a marked delay in the appearance-time of sulfobromophthalein is, however, recorded. The test is of great interest in case of cholostatic cirrhosis (one case).

Whether jaundice is present or not, there are two main types of sulfobromophthalein retention in the blood: (1) retentions by parenchymal hepatic damage associated with sulfobromophthalein elimination time normal or shortened, and (2) retentions due to common bile duct obstruction with a prolonged sulfobromophthalein appearance-time in bile.

The sulfobromophthalein retention due to parenchymal lesion seems related to functional impairment on the vascular side of the hepatic cell. But any particle of the dye reaching the biliary duct system rapidly goes into the duodenum. In cirrhosis, the quickened rate of dye elimination may be due to an increase in the biliary output, to shortening of the liver cell cords, and to proliferation of numerous new bile canaliculi; in the course of hepatitis with jaundice, even though one agrees with our own hypothesis of mechanical obstruction of the canals of Hering, nevertheless, a sufficient number of biliary passages remain open so that the bile and the dye flow rapidly through biliary ducts when the pressure is low.

In jaundice due to incomplete common bile duct obstruction, the sulfobromophthalein blood retention is related to functional inhibition of the biliary side of the hepatic cell because of overpressure in the excretory system. But, in that case, this effect is uniformly spread out over the whole hepatic parenchyma, which explains the delay in the appearance-time of the dye in the duodenum.

JACQUES CAROLI, M.D.

OBSTRUCTIVE AND PANCREATIC PROBLEMS FOLLOWING CHOLEDOCHOTOMY

IN 1938, Lahey suggested that gallstone surgery had evolved through the three stages of cholecystostomy, cholecystectomy, and choledochotomy. Now possibly it has entered a fourth stage, that of dealing with residual problems. External biliary drainage after choledochotomy by means of an indwelling tube (or T-tube) has had a wide vogue. In a recent study, however, I drew attention to the fact that tubal drainage is not always certain drainage and that obstructive jaundice and biliary peritonitis may still occur. Furthermore, the technical problem of an irremovable T-tube, or the fluid and electrolyte imbalance associated with excessive loss of bile may tax the most expert.

The results of a five-year study in 160 cases of drainage of the common bile duct were presented before the Mayo Foundation on Oct. 3, 1952. It indicated that external biliary drainage had occasionally failed to prevent recurrence of obstructive jaundice or to ameliorate with certainty the severe pain of subacute recurrent pancreatitis. During this period I did not use external drainage of the common bile duct for any nonsuppurative conditions but relied on internal biliary drainage (1) by transduodenal choledochostomy if the common bile duct was narrow, or (2) by choledochoduodenostomy if the size of the duct permitted it. Recurrence of obstructive jaundice in the study (whether calculous or noncalculous) was associated with induration of the ampullary portion of the duct as felt with the probe and with induration spreading into the pancreatic head. Internal biliary drainage was applied in 54 of 66 such cases after the common bile duct was opened. There has been no cholangitis, and no further choledochotomy has been required in any of these cases. A drain which led down to a ductal or duodenal suture line was left in place for a few days but the external loss of bile in these cases was negligible.

This use of internal biliary drainage to obviate the sequela of fibrosis in the ampullary region of the common bile duct raised the question of whether a similar approach to the pancreatic duct might obviate subacute recurrent pancreatitis. Ten

From the Sydney Hospital, Sydney, Australia.

cases were selected. The indication for undertaking the procedure was incapacitation due to severe pancreatic pain necessitating daily sedatives or laparotomy as an "acute abdomen."

A malleable probe was passed via a supraduodenal incision into the bile duct and down into the ampullary portion. Transduodenal choledochostomy was then performed with the endothermy needle. Guy sutures were placed in the edges of the incised duct and the ampullary field was lifted anteriorly by bending the tip of the malleable probe. The pancreatic orifice was found and probed in eight cases. In two cases in which the pancreas was hard and shrunken, the search for the orifice was not successful and internal biliary drainage alone was provided without much relief.

In the other eight cases the passage of a fine probe into the pancreatic orifice was not possible until the orifice was incised. A 3 to 5 mm. probe then would be passed for about 6 in. (15 cm.) into the pancreas. In seven cases the orifice was in its usual site about 10 to 15 mm. up from the left side of the ampulla of Vater and in one case the orifice was on the rim of the ampulla itself. This, according to Millbourn,[1] is the usual arrangement—about 86% being medial to the ampulla and 6% being marginal. A portion of the orifice and adjoining ductal wall was removed to provide drainage and free internal biliary drainage was combined with this procedure. None of these patients have required further sedatives. All are well, have good appetites, and have increased in weight. One patient has gone more than 4 years; four more than 2½ years; one, 2 years, and 1, 18 months since operation.

All 10 patients at operation manifested biliary disease either hepatic, cholecystic, ductal, or pancreatic. The histologic findings of the portion of pancreatic duct removed were disappointing except in two cases in which biliary disease was of long standing. In these, marked fibrosis was demonstrable. Littler and Ellis[2] have recently called attention to the close resemblance between the histologic changes of biliary fibrotic disease and those of rheumatoid arthritis. This observation is in accord with that of Womack,[3] in 1944, who emphasized the obstructive as opposed to the inflammatory basis of cholecystitis.

It is not too extravagant to suggest that a hormonal basis governs the development of this fibrotic ampullary syndrome nor to draw attention to the prevalence of carcinoma in this region.

KENNETH W. STARR, F.R.C.S.

1. Millbourn, E.: On the Excretory Ducts of the Pancreas in Man, with Special Reference to Their Relations to Each Other, to the Common Bile Duct and to the Duodenum, Acta anat. **9**:1-34, 1950.

2. Littler, T. R., and Ellis, G. R.: Gall-Stones: A Clinical Survey, Brit. M. J. **1**:842-844 (April 19) 1952.

3. Womack, N. A.: The Origin of Cholecystitis, Surg., Gynec. & Obst. **79**:441-444 (Oct.) 1944.

MELANOSARCOMA

MELANOSARCOMA is a dread disease. Once the diagnosis has really been made, the percentage of cure is very small. Whether the actual number in the lay public is increasing or whether this just appears to be the case because we are seeing more of them at the University Medical Center is hard to determine.

It does seem to me, however, that we are seeing more young people with this type of lesion. In addition, there appear to be more people who have noticed a growth or change in a pigmented lesion following repeated exposure to the sun

and, perhaps, to the irritation of sand on the beach. The over-all rage to get a good sun tan has definitely, I am certain, played a part. Just recently we have seen three people who had had no other trauma to their lesion except repeated severe sunburn, and perhaps some irritation of the lesion while lying on the beach.

My concern is due to the fact that the history of trauma or treatment, so-called, is quite frequently encountered in these patients. We are seeing too many cases where the primary treatment has not been adequate. As far as I am concerned, there is only one adequate treatment and that is wide surgical excision of the subcutaneous tissue and fascia, wherever practical, if one suspects a brownish-black lesion to be a melanosarcoma. X-ray, curette and desiccation, the electric needle, and caustics are all traumatizing types of treatment and are to be condemned. Yet we still see patients who receive that type of treatment and some cases, in fact, in which the specimen has not even been sent to a laboratory for pathologic study.

My plea is that if the individual has a pigmented lesion on the body that is going to be traumatized by his work, clothing, or anything else, it should be surgically excised and studied under the microscope.

Of course, this does not mean that every pigmented lesion on every human body should be removed. If so, we would never have time to do anything else. The ones that are so localized as to be traumatized, however, certainly should be seen by a surgeon who is cognizant of the potentialities of such a lesion. This is especially true of the ones on the palms of the hands and soles of the feet.

H. GLENN BELL, M.D.

TIME AND TIDE

GEORGE B. PACKARD
DENVER

THIS IS my first opportunity to express to you my deep appreciation of the honor of serving as your presiding officer. I feel very humble when I look over the names of the distinguished surgeons who have gone before me in the presidency of this fine and illustrious surgical organization.

It is the duty of a president to deliver an address. This one will be short, and its brevity may be its greatest asset, for you will not all accept the ideas in it—ideas which have concerned me for a long time.

I want to say something about time—it seems more important to me now than it did years ago. May I quote from a recent sea novel, part of a letter from a doctor to his son?

> Remember this if you can—there is nothing, nothing more precious than time. You probably feel you have a measureless supply of it, but you haven't. Wasted hours destroy your life just as surely at the beginning as at the end . . . only at the end it becomes more obvious. Use your time while you have it . . . in making something of yourself.[1]

I want to offer a few thoughts that have troubled me on time spent in medical education, or rather time passed during medical education. No one can oppose the principle that the best possible education is of the utmost importance to every doctor who will later have the privilege and responsibility of protecting human life. But does the doctor—and the public—receive full value for the time spent under the present educational scheme?

Under the conventional eight-four system of education, a student spends eight years in elementary school. In elementary, or grade, school, students are taught basic skills and habits. Certainly 10 per cent of students or more are mentally capable of comprehending this teaching in fewer than eight years. Educators realize this to be true but in general have not worked out satisfactory plans by which highly intelligent students can advance more rapidly than they do at present. Then there is high school with four more years. Here there is another period where growth of body and mind take place, where happiness is sometimes made to seem of greater importance than academic achievement, where ability to make social and other

---

Presidential address, read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

1. Wouk, H.: The Caine Mutiny, Garden City, N. Y., Doubleday & Company, 1951.

adjustments is often considered of more value than the actual courses covered or the grades achieved. The growing youth spends about 38 weeks in school a year during each of these 12 years.

Elementary and secondary schools are not my subject. Our most able educators have studied these teaching levels. I am not in a position to question the assumption that eight years of elementary schooling are necessary, to discuss how overlapping and duplication of subjects in high school and college can be obviated, or to argue whether our present school system postpones maturity. It may not matter that in pre-college years students are taken in convoys, that is, at the pace of the slower ships, as Gregg [2] has phrased it, but I am certain that these convoys, or, as we call them, classes, should not continue for six to eight years longer.

At age 18, the future doctor is ready for college; here we must save some time. Three-fourths of students admitted to medical school in 1951 (according to the 1951 bulletin of the Association of American Medical Colleges [3]) had had four years of college work. Why have three-fourths of the entering medical class taken four years at college? Some students no doubt wished a broad general education, a most worthy ambition. Nonvocational subjects are as essential in medical education as in any other other education if we are to produce sound men and citizens and not simply technicians with no other knowledge beyond their trade. But I am afraid that other students, and perhaps the majority, are not thinking of the value of the humanities. They take four years of college because they believe a bachelor's degree makes them eligible for entrance to a medical school. While only 10 of the 80 medical schools require four years of college work, yet many of the big-name medical schools that list three years as a requirement, have over 90% four-year men in the freshman class. When it is realized that the total number admitted to the medical school 1951-1952 class was 7,381 out of 20,000 applicants, would not any sensible student take his four years at college rather than to chance rejection after three years?

It is apparent that four years of college work are considered in many quarters a necessary or at least a desirable preparation. The medical schools naturally wish to have competent students adequately prepared to profit from medical education and to keep out those intellectually weak and likely to fail. What courses do they require? In general, they ask for an adequate knowledge of the principles and methods of the sciences needed for medical education and as broad a general education as can be added. The specific subjects required by different medical schools show great variation. Chemistry, biology, and physics are almost universal in the lists, though different in amounts. English is named by nearly all, one-half require some foreign language, a few require mathematics. The common denominator of demands is small and would not crowd three college years of any youth of 18 to 21 endowed with ordinary intelligence. It has been stated by experts that two years of college chemistry, one year of college physics, and one year of college biology are all the sciences that should be asked of medical school candidates, plus a common

2. Gregg, A.: Can Excellence be Learned? J. A. Am. M. Coll. **19**:105 (March) 1944.

3. Stalnaker, J. M.: Study of Applicants for Admission to United States Medical Colleges: Class Entering in 1950-1951, J. M. Educ. **26**:1 (Jan.) 1951.

sense selection of English or foreign language courses. That leaves ample time for the broader subjects and ample time for outside activities to make our medical school applicant a well-rounded person.

It would seem no great problem to arrange a three year curriculum to include the common denominator of medical school demands and a broad, but careful, choice of nonvocational subjects that would cover all ordinary personal and social needs. The requirements should be accurately stated and be universal for all medical schools to avoid the risk of the student taking courses simply to impress the entrance committee or courses which are almost a duplicate of those he will have in medical school. Certainly with fewer than 7,500 to be selected from 20,000 applicants, enough quality can be found in the three-year men. If three years of college work is more than adequate, then age should be one of the major factors in choosing freshman entrants—the younger men being favored over the older. Three-year men should thus have a decided advantage over the four.

We have then made one advance toward saving of precious time. One year saved in college for each future medical school graduate equals 5,000 physician work years—not an inconsiderable figure in these times of war demands and claims of physician shortage.

Can we make other savings? After three years in college, the prospective physician is already 21 years old, old enough by standards of growth and mentality to earn his own living and to be a productive member of the community. After all, most young people go out of high school at 18, into full-time jobs, and many reach high and responsible positions.

The next possibility is the four-quarter medical school program allowing graduation in three years. There have been arguments for and against by faculties and students, largely based on the question of overwork.

Against the four-quarter plan is cited the fact that it makes necessary more basic science instructors, and they are hard to find. In addition, it is said, students miss the three-month vacations they have enjoyed ever since entering school. It has been said a student cannot physically endure going to school throughout the year. Furthermore, it is stated, the plan prevents the needy student from earning money during vacation to carry him through the school term.

Arguments favorable have been widely presented. Additional instructors in the basic sciences can be obtained and at a cost less than that of lost time. Laboratory and class room space is utilized instead of being left vacant for 3 months out of 12. Clinical instructors can be recruited from a huge number of clinicians who are anxious to continue their academic affiliations. The teaching load can be divided to leave ample time for research and investigation.

It is necessary to prove the justification for requiring a student to spend an extra nine months or a year in medical school at the loss of medical service. Immediately after graduation, he will enter an internship, probably followed by a residency, where he will rarely have more than two weeks off a year. At age 21, a man should be able to settle down to a year's work as well as at 25. If a medical student cannot physically endure the work of 48 weeks or a little less a year, he probably should choose some less arduous occupation, and there are many, for as a physician he will not for a long, long time have as short a work year. The last and probably

most important problem involved in a full-year medical course is protection of the less financially privileged student. These students include the best; they must not be eliminated. As is already being steadily accomplished, a wider scheme of fellowships and a more comprehensive plan of loan funds are a necessary addition to a straight medical course. It is realized that in the long run, the full year later gained will financially balance or outweigh the earning vacations lost.

Speeding up of medical education is already under trial. One of the outstanding and best-known plans is that of Duke University.[4] This medical school runs on the four-quarter system, 11 weeks to the quarter, or 44 weeks a year, which leaves eight weeks a year for division into vacations—and the plan seems successful. Their dean stated last year that 76% of their seniors at that time had availed themselves of the accelerated program and had completed their course in fewer than four calendar years.

The advantages of the four-quarter system would seem far to outweigh the annual vacation system, if public service is taken into account. This system adds another 5,000 physician work years to medical care—an amount which should not be lost through lack of thought or lack of efficient production.

Can still more be saved? It is not within the scope of my remarks to consider graduate training. A year's internship is universally accepted as necessary to add to the practical knowledge of the graduate. The American Board of Surgery says that four or five years more of a specialized residency is needed to train a surgeon. Such surgeons are realized to be the best qualified that the world has ever known. Perhaps every surgeon does not need a year of research to develop an inquiring mind and perhaps more surgeons can receive at least part of their training away from university hospitals under exceptional clinical tutelage where some outside medical practice can be combined with surgical training. These problems have been considered and are not yet settled.

Dr. Lowell, of Harvard, deplored the constant extension of the period of education and the constant postponement of entrance into active life. According to Dr. Robert Hutchins[5] we have a fatal habit of underrating our juniors, and he points out that young Americans are not inherently immature, that many with very limited formal education have advanced in industry at an early age to positions of great responsibility. In considering medical school applicants and medical school graduates, we must conclude that maturity depends not so much on age as on the system of education and responsibility offered. Before he died at the age of 36, Henry Gray had completed, in addition to other works, his "Treatise on Anatomy," which ever since has been the standard textbook for English-speaking students. When Osler came to The Johns Hopkins University School of Medicine to be Chief of the Medical Service after two previous professorial positions, he was 40 years old; Halstead, Chief of Surgery was 37, and Kelly, Chief of Gynecology was 31.

Before the four or five years ahead to rank as a qualified surgeon, our student even with these two years saved is 24. Is the saving of two years worth while?

4. Markee, J. E.; Harris, J. S., and Davison, W. C.: Programs to Provide More Physicians, J. M. Educ. **26**:437 (Nov.) 1951.

5. Hutchings, R. M.: Education for Freedom, Harper's Magazine (Oct.) 1941.

To be a surgeon or to be a teacher two years earlier may accomplish great things. The total span of productiveness after 29 is all too short. For the individual doctor who spends nearly half his life in school, two extra years salvaged for production seem worth more than the sacrifice required. For the public, 5,000 surgeon work years is a handsome return for 1 year less in college; and an additional 5,000 surgeon work years seems far more desirable than long summer vacations after a student is 21 years old.

These thoughts are not new; they have been expressed many times before. No continuation of school years will put all the desired medical facts into any brain; we cannot all have academic careers; one or more additional years to study the humanities would still be inadequate. We can only try for the most efficient plant to make the most able physicians and surgeons with the least waste of time.

In the 14th century, Chaucer said:

> For time is making
> Stealthy escape, a stream that never again
> Turns to the hills, but glides on to the plain.

227 16th St.

ARE CERTAIN DISEASES ASSOCIATED WITH SPECIFIC BLOOD GROUPS OR RH ANTIGENS?

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ALL MEN interested in medical pathology seem to believe that there is a hereditary factor present in the individual susceptibility to disease. Particularly does this belief apply to the occurrence of pathologic processes of unknown cause.

When the etiology of any one of the idiopathic conditions is finally understood, all physicians may be quite amazed that the simplicity of that etiology remained so long undiscovered.

We feel that all physicians should always be alert to the possibility of occurrence of significant results of presently available common laboratory examinations which might point toward the solution of etiologic problems, even though the tests now seem to apply to entirely different aspects of the disease in question.

With these ideas in mind, we have chosen five pathologic entities of obscure etiology. They are duodenal ulcer, malignant neoplasms of the gastrointestinal tract, chronic ulcerative colitis, chronic cholecystitis with cholelithiasis, and pulmonary embolism proved at necropsy. A study of a series of each of these conditions has been made in an effort to learn whether or not the frequency of occurrence of any of the blood group antigens of the classic ABO system and Rh system varies significantly from normal in any one of the conditions.

We do not wish to imply that before our study we had any reason to believe that the AB or Rh antigens are carcinogenic or that the genes which transmit these antigens from one generation to another also transmit the tendency to the susceptibility to disease. The exact chemical nature of the antigenic substances is as yet unknown. The human blood Group A substance is said to be an amino acid polysaccharide complex.[1]

In so far as is known at present, there are no outwardly observable effects of the blood-grouping genes. However, according to Boyd,[2] there is no fundamental difference between the genes which transmit the blood groups and those which

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From the Division of Surgery, Mayo Clinic (Dr. Mayo); Fellow in Surgery, Mayo Foundation (Dr. Fergeson).

1. Morgan, W. T. J.: Occurrence and Nature of Human Blood-Group Substances, Brit. M. Bull. **2**:165-168 (Oct.) 1944.

2. Boyd, W. C.: Use of Blood Groups in Human Classification, Science n. s. **112**:187-196 (Aug. 18) 1950.

transmit structurally observable characteristics, such as hair color, eye color, finger length, and stature. Logically, the same thought might apply to genes which could possibly carry the predisposition to disease.

It is known that the genes which transmit the various blood group antigens vary in the proportion in which they are present among the peoples of different races. Table 1, compiled from various sources in the medical literature, is presented to illustrate this fact. It can be easily seen from this table that individuals exhibiting differing observable morphologic characteristics of race also may show differing distributions of the classic ABO grouping percentages.

TABLE 1.—*Distribution of Persons of Various Races and Nations According to Blood Group*

Race or Nation	Percentage Distribution			
	O	A	B	AB
United States (Best and Taylor [3])	43	40	13	4
United States (Foord [4])	45	40	10	5
Britain (Alexander [5])	46	38	12	4
All races (Hooper [6])	40.5	35.5	20	4
Eskimo (Boyd [2])	46.5	53.5	0	0
Aborigines (Boyd [2])	48.1	51.9	0	0
Chinese (Boyd [2])	45.9	22.8	25.2	6.1
Russians (Boyd [2])	41.9	27.3	23.3	7.5
Hungary (Bendier and Weizner [7])	35.7	43.3	15.7	5.3
Bushmen (Hooper [6])	50-60	....	....	...
Jews (Hooper [6])	50-60	....	....	...
Negroes (Hooper [6])	50-60	....	....	...
Mongols (Hooper [6])	60-70	....	....	...
Sioux Indians (Hooper [6])	60-70	....	....	...
Chilean Indians (Hooper [6])	70-80	....	....	...
Peruvian Indians (Hooper [6])	70-80	....	....	...

In regard to the presence of the Rh antigens, the same facts seem to be true. Potter [8] has stated that the frequency of occurrence of the Rh positive antigens is much higher in full-blooded Indians and somewhat higher in Negroes than in other races. The incidence of Rh positivity in Chinese and Japanese is nearly 100%, according to Foord.[4] Approximately 85% of the individuals of the Western races are Rh positive.

In a review of the medical literature for approximately the past 30 years, we learned that we are not the first to think of trying to correlate the blood groups with disease occurrence. Of course, much work has been done in the study of the Rh antigens in cases of erythroblastosis fetalis, spontaneous abortion, and transfusion reactions.[8] Some investigators also have found some correlation between

3. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, Ed. 4, Baltimore, Williams & Wilkins Company, 1945.

4. Foord, A. B.: Significance of Results Obtained in Blood Grouping Tests, Ann. West. Med. & Surg. **4**:478-483 (Sept.) 1950.

5. Alexander, W.: An Inquiry into the Distribution of the Blood Groups in Patients Suffering from "Malignant Disease," Brit. J. Exper. **2**:66-69 (April) 1921.

6. Hooper, I.: Origins and Distributions of Blood Groups, Irish J. M. Sc., pp. 382-388, Aug. 1950.

7. Bendier and Weizner: Cited by Pautienis, K., Medicina, Kaunas **18**:1-12 (Jan.) 1937.

8. Potter, E. L.: The Rh Factor in Obstetrics, M. Clin. North America **28**:254-266 (Jan.) 1944.

Rh antigenic sensitivity and mental deficiency in children.[9] We were not able to discover reports of any attempts to determine the relationship of the Rh factor to the diseases which we studied.

Most of the work concerning the relationship of the ABO groups to various pathologic conditions has been done in foreign countries. It is interesting that many authors have reported a prevalence of one blood group or another in association with varying pathologic conditions. Mitra,[10] in 1933, concluded that persons of blood Group AB are more susceptible than others to carcinoma. Johannsen [11] found Groups A and AB to be more prevalent than normal in such patients. Bendier and Weizner,[7] of Hungary, found a greater proportion of Group AB than would be expected in patients with carcinoma. Pautienis [12] reported that German writers found Group O to predominate markedly in patients with hyperthyroidism. He also found that in Lithuania, individuals of blood Groups B and AB seemed to be unusually susceptible to the development of carcinoma. Tagliaferro,[13] in Italy, concluded that persons of Group A are more susceptible to carcinoma. In 1949, Lessa and Alarcão [14] studied a large group of patients in Portugal and came to the conclusion that there is no correlation between disease of any type and the ABO groups.

TABLE 2.—*Distribution of Cases According to Blood Group and Rh Factor*

	Cases					
		Blood Group Percentages				Per Cent Rh
Disease	Number	O	A	B	AB	Negative
Malignant neoplasms of gastrointestinal tract...	935	46.4	40.1	9.4	4.1	16.2
Duodenal ulcer.....	165	47.3	43.0	8.5	1.2	13.9
Chronic cholecystitis with cholelithiasis.....	117	44.4	35.9	15.4	4.3	20.8
Chronic ulcerative colitis.....	87	40.3	37.9	17.3	4.5	8.8
Pulmonary embolism.....	173	46.8	42.8	7.5	2.9	14.4

but that Groups A and B seem to be more prevalent than Group O in cases of neoplastic disease and Group A more common than Group O in cases of gastroduodenal ulcer. On the other hand, Ugelli [15] concluded that Group O was unusually predominant among ulcer patients in Italy.

From the above varying conclusions, it is obvious that every single blood group has been thought to be higher in proportional percentage than would normally be expected among patients with various diseases of unknown etiology. The most common conclusion among the many investigators seems to be that Group AB is elevated in percentage in individuals with carcinoma.

9. Yannet, H.: Importance of the Rh Factor in Mental Deficiency: Preliminary Report, Bull. New York Acad. Med. **20**:512-514 (Sept.) 1944.

10. Mitra, P. N.: The Influence of Blood Group in Certain Pathological States, Indian J. M. Research **20**:995-1004 (April) 1933.

11. Johannsen: Cited by Pautienis, K., Medicina, Kaunas **18**:1-12 (Jan.) 1937.

12. Pautienis, K.: Kraujo grupes ir ju sasyjis su kaikuriomis ligomis, Medicina, Kaunas **18**:1-12 (Jan.) 1937.

13. Tagliaferro, E.: Gruppi sanguigni e carcinoma, Minerva Med. **1**:219-220 (March 4) 1937.

14. Lessa, A., and Alarcão, J.: Contribuição para o estudo das incidências dos tipos do sistema clássico ABO, sobre os estados mórbidos, Hema, Ser. 2, No. 1, pp. 1-32q, 1949.

15. Ugelli, L.: Distribuzione dei gruppi sanguigni negli individui portatori di ulcére gastroduodenali, Policlinico (sez. prat.) **43**:1591-1594 (Sept. 7) 1936.

Having reported on the findings of various authors, we now wish to present our series of cases (Table 2). It is quite obvious that among the cases studied, there is not enough variation from the normal percentage distribution according to blood group to be statistically significant. Particularly does this apply to our study of the group distribution among patients having a malignant gastrointestinal disease. (In our study the term "normal" refers to the percentage distribution for the United States, given in Table 1.)

We do notice that Group B seems to occur with approximately 5% greater incidence than normal in the cases of cholelithiasis and ulcerative colitis in our series, but the number of these cases is too small for this variation to be regarded as important. The same applies to the finding that some 40% of the cases of chronic ulcerative colitis are in Group O, in comparison to the observation that approximately 45% of the other cases are in this group. Probably, if larger series of cases were studied, the varying percentages would fall closely into the found distribution.

The relationship of the presence of the Rh antigens to the same diseases is also demonstrated. The only variations from the reported normal of 85% Rh positivity are found in cases of chronic ulcerative colitis and cholecystic disease; we do not feel that these variations are large enough to be of statistical importance.

One finding was interesting to us. Of five individuals of Group AB who had pulmonary emboli, three were Rh negative. Although the number of persons who are in the Group AB, Rh negative classification is always small, we are planning to watch such patients most carefully in the future for the occurrence of pulmonary embolism, even though the unusually high percentage of Rh-negative persons in our series may be only incidental.

SUMMARY AND CONCLUSIONS

A study of 935 cases of malignant neoplasm of the gastrointestinal tract, 165 cases of duodenal ulcer, 117 cases of chronic cholecystitis with cholelithiasis, 87 cases of chronic ulcerative colitis, and 173 cases of fatal pulmonary embolism has been made in an effort to determine whether or not there is any relationship between the presence of a particular blood group or Rh antigen and the occurrence of these conditions. In agreement with the conclusions of some authors and in contrast to those of others, we do not believe that there is any significant relationship between the studied diseases and the grouping antigens.

SURGERY IN COLONIC DIVERTICULITIS

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DIVERTICULOSIS of the colon is an irreversible structural change that occurs in approximately 5% of persons beyond middle age. Symptoms are absent or inconsequential unless some degree of inflammation supervenes; this constitutes diverticulitis and occurs in an estimated 10% of diverticulosis cases.[1] In the great majority of these cases diet and medication constitute adequate treatment, but complications requiring surgery occur in approximately 1 in every 10 cases of diverticulitis. Such complications are perforation, abscess, fistula formation, obstruction, hemorrhage, and inability to differentiate between diverticulitis and cancer.

The current surgical trend is not toward new procedures in the treatment of these complications, for the fundamental operations have been long established. But modern bowel surgery has been rendered less hazardous by the development of poorly absorbed sulfonamides and antibiotics so that a more radical approach to the problem may decrease the over-all morbidity of the disease without an unreasonable mortality rate.

The preponderance of diverticulitis occurs in the sigmoid colon, where approximately half of the cases of colonic cancer occur, and the problem of the radical approach is concerned chiefly with this segment of the bowel. Nevertheless, complications occur in diverticula of other portions of the colon and are worthy of mention.

APPENDIX

Diverticulitis of the vermiform appendix is commoner than one would expect, though "true" diverticula containing all layers of the wall are less common than "false" diverticula which lack the muscle layer[2]; the latter type is characteristic of diverticula elsewhere in the colon. Acute inflammation of the appendiceal diverticula causes symptoms indistinguishable from acute appendicitis, and its treatment is identical. The diverticula are occasionally opened within the mesentery during the removal of an acutely inflamed appendix.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

1. Smithwick, R. H.: Experiences with the Surgical Management of Diverticulitis of the Sigmoid, Ann. Surg. **115**:969, 1942.

2. Gramse, A. E.; Dockerty, M. B., and Waugh, J. M.: False Diverticula of the Appendix, S. Clin. North America **29**:1189, 1949. Wilson, R. R.: Diverticula of the Appendix and Certain Factors in Their Development, Brit. J. Surg. **38**:65, 1950.

In 1945 at Great Lakes Naval Hospital, a naval officer was operated on for acute appendicitis. The appendix was partially gangrenous and greatly enlarged to about "thumb size" and was deformed by numerous hemispherical diverticula on all surfaces. The specimen was discarded by the pathologist before critical examination of the diverticula was performed.

CECUM

An increasing amount of literature is available regarding diverticulitis of the cecum. The symptoms of this condition are again so like those of appendicitis as to render uncommon a correct preoperative diagnosis.[3] At operation the diagnosis may be confused with adenitis, granuloma, or tumor, and resection of the right colon is often carried out with good results. If the correct pathology is ascertained and the cecal wall is healthy, resection of the diverticulum may be adequate. These are considered to be "true" diverticula, with the muscle layers persisting in the walls.

M. A. C., a 17-year-old girl, was examined 24 hours after the onset of right lower abdominal pain and vomiting. The abdomen was flat but was tender at, above, and lateral to McBurney's point; mild rebound pain was elicited. The leucocyte count rose from 9,900 to 13,200 in six hours, and operation was advised on suspicion of retrocecal appendicitis.

The appendix did not appear inflamed, but a 3 to 4 cm. tumor was found in the mesentery between the appendiceal base and the ileocecal valve. The appendix was removed, and the cecum was opened through the appendiceal base to permit visualization of the interior of the cecum; an ostium was visualized 1.5 to 2.0 cm. below the ileocecal valve. Accordingly, the cecotomy wound was enlarged to include the mass, which was excised and was found to consist of a necrotic diverticulum with a chitinous wall; the wound in the cecum was closed; sulfonamide and penicillin were applied topically; the omentum was fixed to the operative site, and the wound was closed with drains in the superficial layers. Penicillin, aureomycin, and gastric suction were used postoperatively. Convalescence was without event, and it was later determined that the patient was two weeks pregnant at the time of operation, but this did not prevent a normal gestation.

ASCENDING AND TRANSVERSE COLON

Fewer cases of surgical diverticulitis of the ascending or transverse colon appear in reviews.[4] Their presence in association with obstruction of the distal colon may represent a distinct danger due to the possibility of free perforation if the colon becomes distended.

E. A. T., a man, aged 43, was seen in October, 1951. He complained of pain in the right lower abdominal quadrant, which had been present for one week. This pain had been worse while sitting but was relieved by walking or recumbency. His appetite was poor, and he noted belching and bloating in the previous two days. His temperature was 99 F. There was mild tenderness over the cecum and the ileocecal valve. The leucocyte count was 10,200. The urinalysis revealed no abnormalities. A barium enema disclosed a 2 cm. diverticulum of the medial wall of the ascending colon; the appendiceal lumen was patent. He recovered on dietary management.

G. J., a 42-year-old housewife, had midabdominal pains for one year and had lost 54 lb. (24.5 kg.) in nine weeks prior to admission in January, 1950. She had noted a lump in her right flank for several months, but it had been painful only nine weeks. Bloating and vomiting were present for two months. Hematuria was noted once one year previously. She was obese. Her temperature was 102 F. A smooth, rubbery, fixed, slightly tender ovoid mass extended

3. Lauridsen, J., and Ross, F. P.: Acute Diverticulitis of the Cecum, A. M. A. Arch. Surg. **64**:320, 1952.

4. Bosworth, B. M., and Laundan, F. L.: Solitary Diverticulum of the Ascending Colon, Surgery **29**:523, 1951.

from the upper right iliac fossa to the right costal margin, filling the loin and extending nearly to the midline; no bulge was noted in the flank. The abdomen was tender below the right costal margin.

Pyelograms showed right renal calculus with moderate hydronephrosis. Numerous gallstones were visible. X-rays of the colon disclosed an irregularity proximal to the hepatic flexure, with barium escaping from the bowel laterally.

On Feb. 6, 1950, a large right perirenal abscess was drained by a lumbar incision; Escherichia coli and hemolytic Streptococcus were cultured from the pus. X-rays of the colon taken six weeks after operation showed diverticula in the sigmoid and no fistula in the ascending colon.

W. M., a spinster, aged 67, was admitted on April 12, 1952, with her first recognized attack of acute sigmoid diverticulitis. She responded to chemotherapy and to antibiotics and was discharged on medical management, including a mucilaginous bulk agent, two weeks later. She had a prompt exacerbation at home, and obstruction resulted. She was readmitted, and operation was carried out on May 7. She was found to have generalized peritonitis due to the rupture of a previously unsuspected diverticulum of the ascending colon. A tube was sutured into this defect, and several drains were inserted. A stormy convalescent period ensued. A transverse colostomy was formed on June 5. Numerous intraperitoneal abscesses drained spontaneously, and she passed pus per rectum. She was discharged on July 30, and was readmitted three months later. On Nov. 12, the involved sigmoid colon was resected and anastomosed; the colostomy was closed 10 days later. The inflammatory mass about the ascending colon has not totally absorbed, but she has normal bowel action.

SIGMOID

The commonest site of diverticulitis is in the sigmoid.[5] The pathogenesis, in brief, is impaction of the diverticulum, with progressive edema, interruption of blood supply, perforation, and abscess formation. Undoubtedly, perforation may also occur in periods of increased intraluminal pressure in the absence of impaction of the diverticulum. Satisfactory subsidence of diverticulitis and peridiverticulitis, as well as small local abscesses, may be expected while employing the sulfonamides with or without antibiotics in conjunction with a proper dietary and antispasmodic regimen. Larger abscesses will require surgical drainage, as in the past, with reasonable expectation that an external fistula may ensue; the majority of these will close spontaneously in a period of weeks; otherwise, the fistula must be closed below a colostomy, or the segment must be resected and anastomosis performed. If the inflammatory reaction in the adjacent bowel has subsided, the resection may be performed without antecedent or complementary colostomy with little risk.

Abrupt perforation of a diverticulum into the free peritoneal cavity is an unusual and serious surgical emergency.[6] Closure of the perforation must be attended by a defunctioning temporary colostomy in most cases. Exteriorization of the affected segment may be a lifesaving procedure, even though subsequent surgery may be required. Perforation of a diverticulum in the proximal bowel presents a serious problem, since diversion of the fecal stream could only be accomplished totally by ileostomy or by ileocolostomy.

If an abscess perforates into the large or small intestine there will probably be spontaneous subsidence. Perforation into the urinary bladder is not rare but is

5. Albright, H. L., and Leonard, F. C.: Management of Diverticulitis Coli, Am. J. Surg. **82**:674, 1951. Pemberton, J. deJ.; Black, B. M., and Maino, C. R.: Progress in the Surgical Management of Diverticulitis of the Sigmoid Colon, Surg., Gynec. & Obst. **85**:523, 1947. Neal, J. W.: Diverticulitis of the Colon and Its Surgical Management, Surgery **30**:606, 1951.

6. Woodruff, M. F. A.: Spontaneous Perforation of the Large Bowel, Ann. Surg. **135**:221, 1952.

uniformly a serious complication. The passage of pus, feces, or gas from the urethra, with attendant symptoms of bladder irritation, herald this unfortunate sequel. It may be difficult to visualize the fistula either by cystoscopy or sigmoidoscopy, but the use of an opaque medium and roentgenography or the injection of dye in the bladder and visualization through the sigmoidoscope may afford an accurate localization.

Transverse colostomy is of great value in these cases,[7] not only to prepare the bowel for later surgery but to stop the persistent soiling of the bladder and the inevitable infection of the upper urinary tract. Though the fistula may close spontaneously in some cases after diversion of the feces, it is likely to recur on closure of the colostomy unless the affected segment of bowel is removed and the bladder defect properly closed. Only in ideal circumstances has the entire procedure been accomplished in one stage.

E. P., a 63-year-old housewife, complained of painful and bloody urination. In 1945 a laparotomy had been performed for appendicitis, but a large inflammatory mass was found in the pelvis, and the appendix was not removed; postoperative studies of the colon disclosed sigmoid diverticulitis. A wound infection resulted in a ventral hernia. She had a febrile period of several weeks in 1949, due to diverticulitis. In June, 1950, because of acute diverticulitis and suspected pelvic abscess, a transverse colostomy had been performed elsewhere. Postoperatively pyuria and subsequent pneumaturia developed.

X-ray studies after pyelography and after barium enema demonstrated a sigmoidovesical fistula. The inflammatory mass could be felt by rectovaginal examination. The urine was loaded with pus and blood.

On April 4, 1952, the involved 14 cm. of lower sigmoid colon was resected and primary anastomosis performed. The bladder defect was excised and the wall closed. The ventral hernia was repaired. Antibiotics were used before and after operation. Healing was uneventful, and one month later the urine contained only an occasional leucocyte. The healed anastomosis could be palpated by rectum, and the colostomy could then have been safely closed but a combination of personal circumstances prompted the patient to postpone the procedure for several months.

Diverticulitis is not uncommonly associated with blood in the stools and is occasionally the cause of gross hemorrhage. It is of paramount importance to eliminate polyp or carcinoma as a possibility in these cases, as diverticulosis may occur concomitantly with either, although it is likely that no causal relation exists. Profuse, persistent, or recurrent hemorrhage from an area of diverticulitis may properly be eliminated by primary resection and anastomosis after modern preparation of the bowel.

H. L., a woman, aged 63, noted painless rectal bleeding in July, 1952. Proctoscopy revealed blood coming from the bowel above. A barium enema disclosed numerous diverticula, spasm, and narrowing of the sigmoid. Primary resection of 19 cm. of sigmoid colon and primary anastomosis without colostomy were performed after preparation with antibiotics. There was no polyp or carcinoma. The convalescence was uninterrupted, and no further bleeding has been noted.

An inflamed segment of sigmoid may be mistaken for carcinoma of the ovary or for a uterine tumor. When the error is recognized at operation, there is a choice of procedures to follow, dependent upon the severity of the involvement and the symptoms, inasmuch as the patient will probably not have had adequate preparation

7. Bacon, H. E.: Anus, Rectum, Sigmoid Colon: Diagnosis and Treatment, Ed. 3, Philadelphia, J. B. Lippincott Company, 1949.

of the bowel: 1. The abdomen may be closed to institute medical management postoperatively. 2. If the involvement is severe and the likelihood of abscess formation or obstruction is great, a transverse colostomy may be formed. 3. However, one may choose to close the abdomen, institute a period of bowel preparation, and reoperate with resection and primary anastomosis in view, thus eliminating the colostomy period and colostomy closure.

A. M., a woman, aged 58, complained of lower abdominal distress, with cramping and mild nausea of five days' duration, but she had had normal bowel movements. A pelvic examination disclosed a tender 5 cm. mass adherent behind the uterus, and it was presumed that she had carcinoma of the ovary.

Laparotomy by the gynecologists in November, 1949, revealed a 5 cm. segment of inflamed sigmoid colon and numerous diverticula. The abdomen was closed after repair of a defect made by exploring a diverticulum containing a fecalith. After a normal convalescence she did well on medical management but has had three flare-ups of acute diverticulitis, which were treated by sulfonamides or antibiotics. A resection should probably be performed.

The usual characteristics of diverticulitis found on sigmoidoscopy are (1) angulation of the bowel, (2) fixation of the segment, (3) adherence of mucosal folds, (4) spasm, (5) sacculation of the wall, and (6) occasional demonstration of the diverticular ostia. In addition, my colleagues and I have commonly expressed one or more "rabbit stool" pellets of feces from the wall of the bowel immediately beyond the instrument during examination and consider this rather characteristic of diverticulosis. Carcinoma of the lower sigmoid or rectosigmoid can ordinarily be visualized more readily from below, since there is less associated spasm.

In those cases in which the presence of carcinoma cannot be definitely ruled out by endoscopy and roentgenography, resection of the segment should be planned. If obstruction is present in such a case, proximal transverse colostomy is indicated and may be followed by reexamination in the convalescent period when the involved bowel has been rested and cleansed. We feel that the prolonged colostomy period of 6 to 12 months advocated in the past may now be abruptly shortened, as the systemic and local use of antibiotics and low solubility sulfonamides hastens the absorption of the inflammatory reaction.

C. G., a 76-year-old man with mild decompensation of an arteriosclerotic heart, was admitted because of acute colonic obstruction, and a transverse colostomy was performed on Aug. 14, 1952. The nature of the obstructing mass in the sigmoid could not be positively identified before or during operation; x-rays of the colon taken 12 days later disclosed diverticula but could not exclude neoplasm. Superficial femoral thrombectomy and ligation were necessary on Sept. 2. A 1 cm. benign adenomatous polyp of the rectosigmoid was removed by fulguration on readmission. On Nov. 11, 13 cm. of indurated and gnarled sigmoid was resected, and primary anastomosis was performed; no carcinoma was found. Numerous diverticula in the transverse colon were asymptomatic and required no treatment. The colostomy was closed two weeks later, and resumption of normal bowel movements was prompt.

By far the most frequent segment to be resected is the sigmoid colon. Here the natural "S" or sigmoid curve is often sharply angulated by interadherence of the loops so that an acute "Z" forms and accentuates the obstruction from the edematous bowel. Elimination of this segment to provide a straighter tube has seemed to produce satisfactory results in all cases despite the fact that scattered asymptomatic diverticula may not have been eliminated in the descending or transverse colon above. We have not felt compelled to resect the entire left colon and mobilize the transverse colon into the pelvis, as has been done in occasional cases elsewhere.

Nor do we attempt to make an extensive resection of the mesentery for diverticulitis, feeling that resection of the bowel alone with any local mesenteric abscesses is adequate and that the inflamed mesenteric glands will subside spontaneously.

D. B., a dentist, aged 42, began having recurrent attacks of sigmoid diverticulitis while in the Army, in 1943, and was hospitalized on several occasions for conservative treatment. In June, 1950, he again had chills, temperature to 104 F., left lower abdominal pains, diarrhea, and anorexia. He had lost 20 lb. (9 kg.) on admission in August, after having intermittent treatment with streptomycin. Preoperative treatment included the administration of sulfasuxidine, dihydrostreptomycin, and aureomycin. His temperature was normal after 11 days, and two weeks later the involved 12 cm. of sigmoid colon was resected and was found to include a strip of apple peeling within an intramural abscess, as well as numerous diverticula; the bowel was anastomosed and a cecostomy tube was inserted; this was removed in one week, and he left the hospital three days later. His bowel complaints have been relieved; a small hernia persists at the cecostomy site.

A. D., a woman, aged 66, was hospitalized for diverticulitis of the sigmoid in March, 1946, and improved while taking sulfasuxidine for a prolonged period. Repeated sigmoidoscopic and fluoroscopic examinations during the subsequent four years revealed no neoplasm. A tender induration of the lower sigmoid never completely subsided, and the stools became smaller in caliber, constipation was moderate, and cramps and bloating recurred intermittently despite proper medical management.

On Feb. 24, 1950, at operation, the sigmoid loops were found to be interadherent, doubling the bowel upon itself at several points; the bowel wall was characteristically indurated. A resection of 14 cm. of sigmoid was followed by primary anastomosis without colostomy; several diverticula in the descending colon were not treated; convalescence was not unusual. A postoperative hernia was repaired in November, 1951, and she has remained well.

After a few experiences with cecostomy or sigmoid colostomy for this disease, we have become convinced of the wisdom of the current advocacy of transverse colostomy. This is a less convenient colostomy to care for than one in the left colon, but the waiting period can now be shortened, and its many advantages are obvious.[8]

In the absence of obstruction or abscess, a resection of the sigmoid colon can be undertaken as a one-stage procedure with increasing safety as the effectiveness of modern antibiotics increases. This is shown by the series reported from the Portland Clinic by Boyden in which 32 sigmoid resections for diverticulitis were performed without mortality; 25 of these were performed as primary anastomoses without complementary or antecedent cecostomy or colostomy.[9] Low mortality rates for similar procedures are reported by Smithwick, Pemberton, and others. Smithwick has demonstrated that less than radical surgical treatment eventuates in 60% poor results, as compared with 84% successes in resected cases.

COMMENT

The surgical treatment of diverticulitis has long been directed at the treatment of the various complications that arise either without or in spite of medical management and are somewhat reminiscent of the disadvantage of too long postponed surgery in ulcerative colitis. Certainly some of these complications can be predicted as progression of the disease or failure of medical management becomes obvious, and

8. Albers, J. H., and Smith, L. L.: A Comparison of Cecostomy and Transverse Colostomy in Complete Colon Obstruction, Surg., Gynec. & Obst. **95**:410, 1952.

9. Boyden, A. M.: The Surgical Treatment of Diverticulitis of the Colon, Ann. Surg. **132**:94, 1950.

it is in such cases that primary resection and anastomosis may then be offered as an elective procedure, with the prospect of preventing prolonged disability and the economic shock of long hospitalization.

SUMMARY

The complications of diverticulitis as they occur in various segments of the colon are discussed. Eleven case reports are presented to illustrate various problems and methods of surgical treatment.

The therapeutic accessories to modern colon surgery permit an increasingly radical approach to diverticulitis of the sigmoid colon.

DISCUSSION

DR. VICTOR E. CHESKY, Halstead, Kan.: I should like to discuss the last paper. I was particularly interested in the last part of Dr. Patton's remarks.

Recently I have had two patients that came in with a partial obstruction of the sigmoid, and both had had frequent attacks of lower left quadrant abdominal pain over a period of years, the cause of which really never was diagnosed.

When they came in, they had a rather high degree of obstruction that required decompression. Our roentgenologist rather suspected that in one case the condition was not malignant, but in the other he could not make a definite diagnosis.

After decompression both patients were operated on, and a benign cicatricial stenosis of the sigmoid was found. In the one patient with a high degree of obstruction this cicatrix was very thick, with a very small pencil-sized opening through the sigmoid. The fibrous tissue apparently developed during the repeated attacks of diverticulitis.

SURGICAL TREATMENT OF STRICTURE OF THE COMMON AND HEPATIC BILE DUCTS

A Twenty-Eight-Year Survey

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AND
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ROCHESTER, MINN.

ON PREVIOUS occasions one of us (Walters) has presented studies of 165 patients with stricture of the common and hepatic duct operated on from 1924 to 1947 inclusive.[1]

The present study is based on 100 patients on whom 113 operations were performed from 1948 through 1951. In this group were 11 patients on whom one of us (Walters) had previously operated for stricture.[2] The operative mortality rate was 7.1%.

Since a thorough study of the cases prior to 1949 was presented at one of the meetings of a surgical association at that time and subsequently, in this presentation we shall confine our discussion principally to our recent study of patients operated on from 1948 through 1951, and shall reserve until another occasion a detailed comparison of the different groups of cases.

In Table 1 are recorded the different types of surgical procedures used, the number of cases in each group which have been followed for more than one year, with the results of the operation, the percentage of evidence of recurring biliary obstruction, the hospital deaths, and deaths later.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

From the Division of Surgery, Mayo Clinic (Dr. Walters); Fellow in Surgery, Mayo Foundation (Dr. Kelly).

1. Walters, W., and Lewis, E. B.: Strictures of the Common and Hepatic Bile Ducts with a Report of 98 Cases, in Lahey, F. H.: Frank Howard Lahey Birthday Volume, June First, Nineteen Hundred Forty, Springfield, Ill., Charles C Thomas, Publisher, 1940, pp. 443-457. Walters, W.: Physiologic Studies in Cases of Stricture of the Common Bile Duct, Ann. Surg. **130**:448-454 (Sept.) 1949. Walters, W., and Phillips, S. K.: Physiologic Aspects of Repaired Stricture of the Extrahepatic Bile Ducts: Report of 165 Cases, Proc. Staff Meet., Mayo Clin. **24**:12-16 (Jan. 5) 1949; Stricture of the Bile Ducts, in Christopher, F.: A Textbook of Surgery, Ed. 5, Philadelphia, W. B. Saunders Company, 1949, pp. 1152-1161. Walters, W., and Marvin, C. P.: Complete Stricture of the Extrahepatic Bile Ducts: External Hepaticostomy Followed by Spontaneous Hepatoduodenal Fistula, Arch. Surg. **57**:18-23 (July) 1948.

2. Walters, W., and Cameron, J. M.: Studies of Biliary Strictures and Their Surgical Treatment in 184 Patients, Proc. Staff Meet., Mayo Clin. **25**:150-156 (March 29) 1950. Walters, W.: Symposium on Abdominal Surgery: Strictures of the Common and Hepatic Bile Ducts and Their Treatment, S. Clin. North America **30**:987-1000 (Aug.) 1950.

More than half (61, Table 1) of the patients in the 1948 to 1951 series had direct anastomoses of the common or hepatic duct to the duodenum. In nine cases the stricture involved so much of the common hepatic bile duct that it was necessary to dissect both hepatic ducts from the hilus of the liver and to anastomose them to the duodenum or jejunum. In 30 patients (26.5% of 113 operations) direct anastomoses were made between the ends of the duct after excision of the strictured areas. The percentage of the total in which this operation has been performed has increased progressively from 11.2% (11 patients) in the 1924 to 1939 group to 18.6% (16 operations) in the 1940 to 1947 group, and 26.5% (30 operations) in the 1948 to 1951 group (Table 2).

TABLE 1.—*Results According to Operation: For Stricture of Common and Hepatic Ducts: 1948-1951*

Anastomosis or Operation	Cases	Hospital Deaths		Patients Traced More Than 1 Yr.	Well		Had Recurrence		Died	
		No.	% *		No.	% *	No.	% *	No.	% *
Hepatic duct to duodenum	46†	3	6.5	32	17	53.1	11	34.4	4	12.5
Hepaticojejunostomy	6	0	0.0	1	0	0.0	1	100.0	0	0.0
Common duct to duodenum	15	3	20.0	7	5	71.4	2	28.6	0	0.0
Duct to duct	30	0	0.0	21	15‡	71.4	5§	23.8	1	4.8
Hepaticostomy	8	2	25.0	6	1	16.7	3	50.0	2	33.3
Total	105‖	8	7.6 (7.1¶)	67	38	56.7	22	32.8	7	10.5

* Per cent of patients traced.
† Nine patients had double hepaticoduodenostomy (2 were well).
‡ McArthur method in 2 cases.
§ McArthur method in 4 cases.
‖ Some patients appear in more than one category; hence total 105, although only 100 patients were treated 113 times. Eleven of these patients had been operated on by Dr. Walters previous to 1948.
¶ Per cent of 113 operations.

TABLE 2.—*Type of Operation for Stricture of Biliary Ducts: 1924-1951*

Anastomosis or Operation	1924-1939		1940-1947		1948-1951		Total	
	Patients	%	Operations	%	Operations	%	No.	%
Hepatic duct to duodenum	31	31.6	39	45.4	51	45.1	121	40.7
Hepaticojejunostomy	..	....	..	....	6	5.3	6	2.0
Common duct to duodenum	34	34.7	10	11.6	15	13.3	59	19.9
Duct to duct	11	11.2	16	18.6	30	26.5	57	19.2
Hepaticostomy	9	9.2	11	12.8	11	9.7	31	10.4
Other operations	13	13.3	10	11.6	..	....	23	7.8
Total	98	100.0	86	100.0	113	100.0	297	100.0
Patients	98	....	67	....	100*	....	254	....

* Eleven of these patients had been operated on by Dr. Walters for biliary stricture previous to 1948.

In 1948 to 1951 the results of the operation (Table 1) were practically the same, namely 71.4% were well more than a year, when (1) an accurate anastomosis was made between the common duct and the duodenum and (2) when the anastomosis was made between the ends of the ducts. The incidence of recurrence in the two groups appears to be similar also (approximately 25%).

When the stricture was so extensive that a short segment of the common hepatic duct was not readily available for an anastomosis, necessitating dissection into the

liver substance to obtain it, with much more difficulty in performance of an accurate biliary intestinal anastomosis, the number of patients well without requiring a second operation decreased to 53.1%, and recurrent symptoms occurred in 34.4%.

The problems in the correction and treatment of stricture of the bile ducts are two: (1) the identification and dissection of sufficient length of common or hepatic bile ducts to make an accurate anastomosis between the ends of the ducts beyond the stricture or between the upper end of the duct and the duodenum or jejunum, and (2) the prevention of contracture of the anastomosis.

FINDING THE DUCT ABOVE THE STRICTURE

With the passage of years and an increasing experience, it has been possible to identify and dissect a greater number of duct ends for duct-to-duct anastomosis, and in cases in which the lower end of the duct could not be identified to obtain a sufficient length of the hepatic bile duct above the stricture to increase the percentage of anastomoses of the hepatic duct to the intestinal tract (Table 2). The most valuable aids in this procedure have been, first of all, dissection of the hepatic flexure of the colon and the duodenum from the under surface of the right lobe of the liver in order to expose the lateral aspect of the hepaticoduodenal ligament, and, likewise, dissection of the stomach and omentum from the under surface of the liver, exposing the hepatic artery on the mesial aspect of the hepaticoduodenal ligament.

The first assistant places the middle and forefingers of his left hand over the patient's hepaticoduodenal ligament and pulls downward. The pulsating hepatic artery becomes clearly visible, and the outer margins of the hepaticoduodenal ligament are definitely defined. The liver is retracted upward and outward to expose the hilus by one assistant with the use of two Deaver retractors. The duct not involved in the stricture lies in this region. It frequently can be seen [3] but occasionally is located by means of an aspirating needle. The aspirating needle also will keep one from inadvertently opening the portal vein or cutting into the right hepatic artery. When the uninvolved stump of the bile duct has been located, it is opened and then cut across. Allis forceps are placed on its open end, and with the aid of traction and dissecting scissors dissection can be carried into the liver parenchyma at the hilus. This will usually give an additional 6 to 8 and sometimes 10 mm. of length to the stump of the duct, and make an accurate anastomosis to the intestines possible. If, in the course of dissection of the stump of the duct, a small opening is made into the portal vein or the right hepatic artery, bleeding should be immediately controlled by the use of a small silk suture swaged into the end of a small curved needle.

PREVENTION OF CONTRACTURE

In the early experience of one of us (Walters) in an occasional case in which the common bile duct above the stricture was quite large, the anastomosis of the common or hepatic duct to the duodenum was made without prosthetic devices in its interior. Since that time, evidence accumulated has seemed to indicate that the presence of a hollow tube maintained within an anastomosis for a period longer than three months decreases the incidence of contracture of the anastomosis.

3. A drop or two of bile frequently will indicate the location of the duct when an impending fistulous tract to the duodenum is trying to develop.

Generally, the end of an inlying rubber urethral catheter has been passed through the forcibly dilated sphincter of Oddi into the duodenum (the upper end above the anastomosis) to serve as a splint when a duct-to-duct anastomosis has been made, and pieces of catheter with oversized rings (Mayo-Sullivan tube) or T-tubes have been used to splint the anastomoses between the common or hepatic duct and the duodenum or jejunum. The indwelling tubes (except the T-tubes) have been maintained in position with a silk suture passed through them and brought out through the incision and attached to a button on the abdominal wall as recommended by McArthur. Without such anchoring, peristalsis pulls the tube from the anastomosis into the intestinal tract and it is passed in the stools.

When the patient has been deeply jaundiced and there is a good deal of infection and stony material in the intrahepatic ducts, the T-tube has been used to splint the anastomosis and to permit complete drainage of the intrahepatic ducts. Whenever possible, attempts have been made to bring the vertical part out through a small longitudinal incision in the duct extending from the site of the anastomosis, but seldom is there sufficient duct to do more than bring the tube out from the anterior portion of the anastomosis itself.

TABLE 3.—*Analysis of Procedures (Operations): 1948-1951*

Anastomosis	Operations	Prostheses Used			
		T-Tubes	Mayo-Sullivan Tube	Catheters	None
Hepatic duct to duodenum	51*	31	20	0	0
Common duct to duodenum	15	2	10	0	3
Duct to duct	30	22	0	8	0
Hepaticostomy	11	0	0	9	2

* Nine of these were double hepaticoduodenostomy.

It has been thought best to keep all prosthetic devices in place for at least nine months. In cases in which there was considerable infection within the liver and a T-tube has been used in the anastomosis it has seemed advisable to irrigate the ducts frequently through the T-tube to keep it open for the passage of bile into the duodenum and also to prevent the accumulation of bile pigment debris within the dilated intrahepatic ducts during the early period after the operation. Other prosthetic devices, such as polyethylene tubes made into the shape of Mayo-Sullivan tubes, and vitallium® tubes, have been used, but unfortunately bile pigment accumulates sooner or later within the lumina of all of them, and they either must be made to pass from the anastomosis or removed surgically because they will all act as foreign bodies and obstruct the bile duct.

The types of prosthetic devices used in the different operative procedures performed are given in Table 3.

RECURRING BILIARY OBSTRUCTION AFTER BILIARY INTESTINAL ANASTOMOSIS

On previous occasions one of us (Walters [2]) has commented on the fact that cholangitis or symptoms suggesting it, developing after operations for stricture, were the result of contracture of the anastomosis and not the result of reflux of food or secretion, gases or bacteria from the duodenum through the anastomosis into

the biliary tree. We have not on any occasion failed to find varying degrees of anastomotic contraction in such cases in which another operation has been performed. Even though the entire triad of symptoms—biliary colic, chills, and fever—may have been lacking, at least one or more of these symptoms were present. We have repeatedly seen contraction of the duct at the anastomosis to a diameter of only a few millimeters when the patient's only symptom was intermittent attacks of pain.

The indication for reoperation, therefore, is a return of repeated attacks of biliary obstruction, especially if jaundice, fever, or chills are associated with the attacks of pain. In many of our cases at least one attempt at repair of the stricture, and in some more than one, has been made. Indeed, one of us (Walters) has had to reoperate on 11 patients on whom he had performed operations before 1948 for stricture. Yet in our experience, regardless of how many unsuccessful operations for repair of the stricture may have been performed previously, it still may be possible to obtain a satisfactory result if the liver is not so badly damaged by cirrhosis that decompensation has resulted. The operative risk in the presence of hepatic decompensation, however, is so high that it is almost prohibitive.

PREOPERATIVE AND POSTOPERATIVE TREATMENT

Time does not permit more than the briefest reference to preoperative and postoperative treatment of the patient with stricture of the duct. It seems trite, but it is still important, to mention that all jaundiced patients to be operated on should have determinations of prothrombin time and blood urea, at least one or two tests of liver function, and also if possible a determination of albumin-globulin ratio. All of the jaundiced patients should receive vitamin K before and after operation, and an abundance of carbohydrate or glucose. Sufficient blood should be cross matched and made available so that it can be administered to the patient at or immediately after operation, if necessary.

Almost without exception we have used general anesthesia with a combination of oxygen, nitrous oxide, and ether in our cases. The intravenous administration of preparations of vitamin K, sufficient fluids and glucose to maintain a proper fluid and electrolytic balance, and the control of anemia are essential to good postoperative care.

When T-tubes have been inserted, they are gently irrigated by gravity with sterile water twice weekly to keep them open and free of bile pigment debris.

SUMMARY AND CONCLUSIONS

This report is concerned for the most part with 100 patients on whom 113 operations were performed by one of us (Walters) at the Mayo Clinic from 1948 through 1951. The hospital mortality rate by operations was 7.1%. One of us (Walters) had operated on 11 of the 100 patients for stricture of the bile ducts prior to 1948.

Direct anastomosis between the common or hepatic duct and the duodenum was possible in more than half (61) of the cases. Both hepatic ducts were dissected from the hilus of the liver and anastomosed to the duodenum in nine cases because the stricture involved so much of the common hepatic bile duct.

Direct anastomosis between the ends of the duct was performed after excision of the strictured portion in 30 cases. The percentage of cases in which this operation

was employed has increased over the years. It was performed on 11.2% (11 patients) of the group operated on for biliary stricture from 1924 through 1939, at 18.6% (16 operations) of the operations for stricture from 1940 through 1947, and at 26.5% (30 operations) of the operations for stricture from 1948 through 1951.

Results of each type of operation performed in the years 1948 to 1951, inclusive, were determined one year or more after operation. End-to-end anastomosis of the duct and anastomosis of the common duct to the duodenum gave practically the same results: 71.4% of the traced patients in each group were well, and 23.8 and 28.6%, respectively, had recurrences. Anastomosis of the hepatic duct to the duodenum did not give quite such good results, as only 53.1% of the patients were well. This difference was usually due to the difficulty of making an accurate anastomosis and to more hepatic damage and infection. In these cases there had been extensive involvement of the ducts which frequently necessitated dissection into the liver in order to obtain sufficient duct for the anastomosis.

Previous operations for biliary stricture which have been followed by recurrences of obstruction are not contraindications to further operations even in the presence of cirrhosis of the liver with collateral circulation. Indeed additional operations even under these circumstances may yield better and longer-lasting relief. In the presence of hepatic decompensation, however, the operative risk is exceedingly high and the benefits of relief of the obstruction are questionable.

EXPLORATION OF THE COMMON BILE DUCT

Analysis of One Hundred Cases

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WE ARE reporting from the Surgical Service of the University of Colorado School of Medicine 100 consecutive cases of exploration of the common bile duct in an effort to determine the positive incidence of choledocholithiasis, and the relation between jaundice and choledocholithiasis; and to determine whether choledocholithiasis develops as a new condition following previous cholecystectomy. In 290 cholecystectomies, choledochotomy was performed 100 times, or 34%.

In no instance in this series—as proved by the necessity for reexploration—was there failure to explore a duct which was obstructed by calculus. In three instances,

TABLE 1.—*Common Duct Exploration, 1947-1951*

		No. of Cases
Total cases of exploration		100
Stones found at initial exploration	47	
Stones found at subsequent operation, same admission	3	
Stones found at autopsy, same admission	1	
Total positive		51
Total negative		49

reexploration of the duct was required to correct obstruction which had not been relieved at the initial operation. Our error, then, has not been attributable to our criteria for exploring the common duct, but rather to our failure to make sure of removing all obstructing calculi which were present (Table 1).

If there is doubt that a patent duct system is present at the conclusion of exploration, as evidenced by the free flow of bile from above and an unobstructed passage to the duodenum below, a cholangiogram should be taken while the patient is on the table. For the great value of a cholangiogram is to obviate the necessity of second exploration when postoperatively the clinical triad of persistent jaundice, clay-colored stools, and profuse T-tube drainage gives conclusive evidence of continued common duct obstruction.

The surgeon has two opportunities to anticipate the presence of calculi in the common bile duct. The first occurs preoperatively, when obstructive jaundice is

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From the Surgical Service of the University of Colorado School of Medicine and the Colorado General Hospital.

present. Yet obstruction by calculus is not the commonest cause of jaundice, nor is it at all times possible by the most astute clinical and laboratory methods to differentiate the obstructive from the nonobstructive type of jaundice. Secondly, at operation, the surgeon can examine certain physical signs in the biliary tract which may indicate the presence of calculus in the common duct. These signs include palpable stone in the duct, dilated common duct, thickened duct, and contracted gall bladder with stones and a large cystic duct. These signs should be utilized by the surgeon even in those cases with jaundice or with a history of jaundice, as the incidence of positive findings in this group of cases is only slightly higher than in the group without jaundice (Tables 2 and 3).

TABLE 2.—*Cases in Which Jaundice Was Diagnosed Clinically*

	No. of Cases	
Total cases with jaundice		60
Duct contained stones		33 (55%)
Jaundice not due to stones		27 (45%)
Dilated common duct	9	
Normal duct	8	
Stenosis of duct	2	
Dilated duct with sediment	3	
Toxic hepatitis	2	
Edema of common duct; acute cholecystitis	2	
Cirrhosis, biliary	1	
Total without stones	27	

TABLE 3.—*Choledocholithiasis Without Clinical Jaundice*

	No. of Cases	
Total ducts explored in cases without clinical jaundice		40
Total positive for choledocholithiasis		18 (45%)
Elevated serum bilirubin (below level clinical jaundice)	5	
Small contracted gall bladder, dilated cystic duct, dilated common duct, palpable stone in duct	13	

In the future we intend to do liver biopsies in all cases with jaundice in which, in spite of positive physical signs for exploration, results of exploration have been negative. However, particularly in cases of diminishing jaundice, an obstructing calculus may have passed into the duodenum. Certainly many calculi must pass through the common duct in an asymptomatic manner, and perhaps for these puzzling cases no further explanation will be forthcoming than that a calculus has moved on.

There were five deaths in this series (Table 4). All five patients who died were deeply jaundiced. In Cases 1, 4, and 5 the patients were in very poor preoperative condition, and operation was decided upon as a desperation measure. These patients might have been operated upon earlier in their illness, or a less radical drainage procedure—cholecystostomy—might have been tolerated. Case 2 illustrates the hazard of operating in a case of toxic hepatitis.

There was no mortality in the group of cases without severe derangement of liver physiology—either in the group in which results of common duct exploration

were negative or in the group in which a nonobstructing calculus was removed. Exploration of the common duct, then, in our experience, has not increased the mortality rate in cases without jaundice.

Nor has the incision of the duct for exploratory purpose led to subsequent obstructing cicatrix of the common duct (Table 5). The two cases of stenosis which were encountered followed simple cholecystectomy. Of the seven cases in which cholecystectomy had previously been done and in which the occasion for reexploration was a question of common duct obstruction, calculi were discovered in two. In these two cases cholecystectomy had been done elsewhere, 16 and 22 years ago,

TABLE 4.—*Summary of Cases in Which Death Followed Exploration of Common Bile Duct*

Case No.	Sex	Age	Preoperative Data	Operative Findings	Time of Death, P. O. Day
1	F	53	Deeply jaundiced; uncontrolled diabetes	Common duct stone	10th
2	F	30	Jaundiced	No stone in gall bladder or common duct; necrosis of liver	6th
3	M	52	Previous (16 yr.) cholecystectomy; jaundiced 3 wk.	Atresia of ampulla due to impacted stone; choledochogastrostomy which never functioned	11th
4	F	78	Deeply jaundiced	Stone in common duct	9th
5	F	67	Semicomatose; deeply jaundiced	Calculi in common duct	10th

TABLE 5.—*Previous Biliary Tract Surgery*

	No. of Cases
Cholecystostomy	9
Cholelithiasis	9
Common duct stone	5
Cholecystectomy	7
Common duct stone	2
Carcinoma of gall bladder	1
Normal common duct	2
Stenosis requiring plastic procedure	2

respectively. Whether indications were present at that time for exploration of the duct, we do not know, nor is it possible to state whether these calculi had been present asymptomatically since cholecystectomy or whether they formed as a new entity.

In either event, among the patients who have undergone cholecystectomy the percentage to come to operation with choledocholithiasis is small. This low incidence of common duct calculus is consistent with the concept that the gall bladder is the locus for the formation of biliary tract calculi, and that with this source removed and the common duct cleared of calculi which are concomitantly present further formation of calculi is the exception.

T-tube drainage of the common duct, with the tube left in situ long enough for the development of an external biliary fistula—considered to be a minimum of 12 days—was the policy followed in this series of cases.

LIVER FUNCTION AS DETERMINED BY SERUM CHOLINESTERASE ACTIVITY

Studies in Patients Undergoing Surgery on the Biliary Tract

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AND
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THE ENZYME cholinesterase is a protein of liver origin. The concentration of cholinesterase appearing in the blood serum at any one time is a reflection of the rate of formation of the enzyme by the liver. The value of the determination of the cholinesterase activity of the blood serum as an index of liver function in various pathological states has been reported by many. Our preliminary observations on its value as a liver function test in surgical patients have been previously reported.[1]

This report is concerned with studies conducted on an additional 49 patients, all of whom underwent surgery on the biliary tract. In these patients serum cholinesterase levels were determined on one or more preoperative days, immediately before and immediately after the surgery performed, and on the 1st, 2d, 3d, 4th, 5th, 7th, and 10th postoperative days. Hemoglobin levels were determined simultaneously. Laboratory determinations of serum cholinesterase activity, hemoglobin content, and all other blood components mentioned in this report were made by the same methods referred to in the previous report.[1] One unit of cholinesterase activity is the milliliter of 0.01 N sodium hydroxide needed to neutralize the acetic acid liberated by 0.5 ml. of serum from 25 mg. of acetylcholine chloride in 10 ml. of carbon-dioxide-free water in 10 minutes at pH 7.8 and temperature of 37 C.

Since our preliminary report, further studies have been made on normal controls. Distribution data on 848 determinations on 225 controls are shown in Chart 1. Normal values vary within a wide range, and there is a significant difference between the levels in males and females. The average value for males is 2.43 and that for females 2.21 units.

Hemoglobin findings were included in this study because we had previously shown that the serum cholinesterase level fell with hemorrhage and rose rapidly if the blood loss was replaced immediately after the hemorrhage, but rose slowly if

From the H. L. Snyder Memorial Research Foundation.

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1. Snyder, H. E.; Snyder, C. D., and Bunch, L. D.: Serum Cholinesterase Levels in Surgical Patients, Am. Surg. **17**:959-981 (Oct.) 1951.

the anemia had been present for more than a short period. In the present group of patients, hemoglobin levels were maintained at near normal, and no significant observations could be made from the data.

Chart 2 demonstrates graphically the average depression of serum cholinesterase activity in 44 patients undergoing cholecystectomy. In 20 of these, choledochostomy

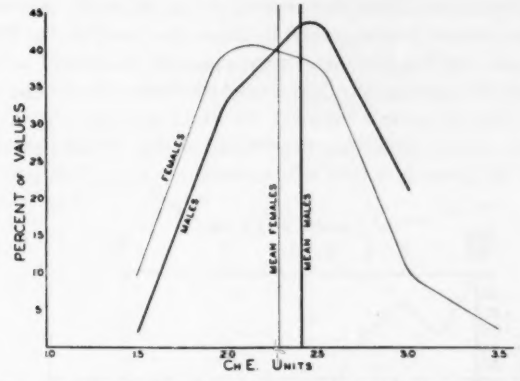

Chart 1.—Distribution of healthy controls (100 males, 125 females).

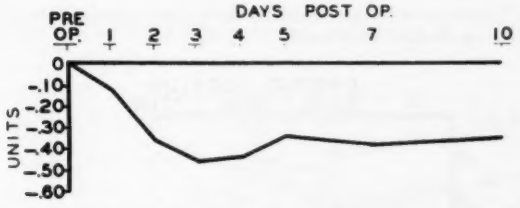

Chart 2.—Average depression of serum cholinesterase activity following biliary-tract surgery.

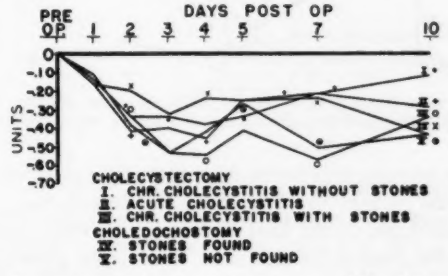

Chart 3.—Average depression of serum cholinesterase activity following biliary-tract surgery.

was performed. It may be seen that the average greatest depression was encountered on the third and fourth postoperative days. After this there was a definite improvement in the average level, but on the 10th day the cholinesterase activity averaged 0.35 units below the preoperative average. Chart 3 presents data obtained after dividing the 44 cases into five subgroups, depending upon the diagnosis and the

surgery performed. It was rather surprising to find that in those patients having choledochostomy the fall in serum cholinesterase activity following surgery was less in those patients in whom stones were encountered than in those in whom no stones were found. However, those having common duct stones had an average preoperative level of serum cholinesterase which was 0.3 unit less than the average in the group in whom no stones were found in the common duct. One might assume from this information that removal of stones from the common duct and drainage of the duct with a T-tube tended to lessen the insult to the liver, whereas, choledochostomy performed upon the normal common duct only added insult to the liver. In most of the patients who had choledochostomy the T-tube was removed from the common duct sometime between the sixth and the eighth day. These patients all showed greater persisting depression of the cholinesterase activity on the 10th day than did those in whom cholecystectomy alone was performed.

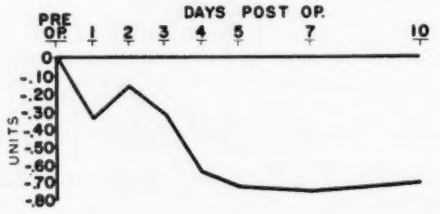

Chart 4.—Average depression of serum cholinesterase activity following biliary-tract surgery in patients with complicating diseases (five cases).

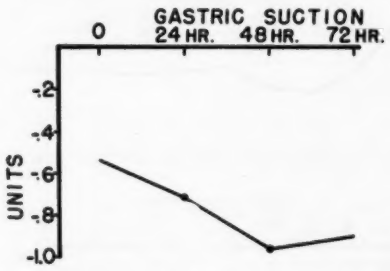

Chart 5.—Average greatest depression of serum cholinesterases activity in patients undergoing biliary-tract surgery, as related to period nasogastric tube was employed.

Chart 4 shows the average depression of serum cholinesterase activity in five patients with biliary tract surgery in whom there was complicating disease. Three of these patients had cirrhosis of the liver and one underwent choledochojejunostomy for carcinoma of the head of the pancreas. One of the patients with cirrhosis of the liver also had wound dehiscence on the fifth postoperative day. It may be seen from this Chart that there is no evidence of recovery of serum cholinesterase activity as late as the 10th postoperative day and that the average fall was much greater than in any of the other groups of cases.

Chart 5 demonstrates graphically the depression in cholinesterase activity as related to the employment of the nasogastric tube. In 33 of the patients the nasogastric tube was not used, and the average greatest depression of serum cholin-

esterase activity was 0.54 units. In the nine patients in whom the tube was employed for 24 hours or less, the average depression was 0.72 units. In four patients in whom the tube was employed for more than 24 hours and not more than 48 hours. the average depression was 0.97 units. In three patients in whom the tube was down more than 48 and not more than 72 hours, the average depression was 0.91 units. It is our custom to employ the nasogastric tube only in those patients in whom distention is expected or in those in whom gastric distention develops. In the 16 patients in this series in whom the nasogastric tube was used, it was placed immediately after operation in 12, on the first postoperative day in 2, and on the second postoperative day in 2. One, of course, would expect lower serum cholin-

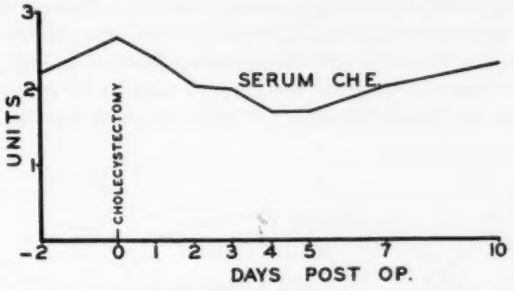

Chart 6.—Serum cholinesterase levels in Patient E. B., man, aged 51, with chronic cholecystitis and cholelithiasis for which cholecystectomy was performed.

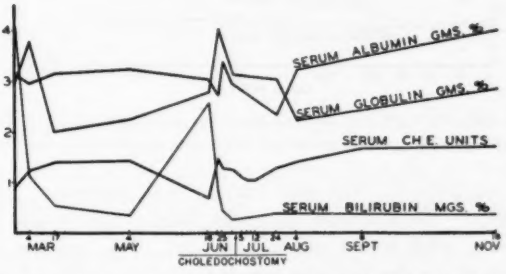

Chart 7.—Serum albumin, globulin, and bilirubin levels in Patient M. O., woman, aged 80, with choledocholithiasis.

esterase levels in the sicker patients in whom it seemed wise to employ the nasogastric tube or in whom its use became necessary. Any complication delaying oral intake of food seemed to lead to added depression of serum cholinesterase activity and to delay of its replenishment.

Chart 6 shows the serum cholinesterase levels in a rather typical uncomplicated case of chronic cholecystitis and cholelithiasis in which cholecystectomy was performed. On the evening of the surgical day this man sat on the edge of his bed, and on the first postoperative day he was out of bed and walked in the hall and took tea and water by mouth. On the second postoperative day he took liquids until the evening meal, when, being hungry, he was given a low-fat, soft diet. The

lowest serum cholinesterase levels were on the 4th and 5th days, but considerable improvement was noted on the 7th day, and the level on the 10th day was certainly within normal limits.

An entirely different sort of picture is found in Chart 7, which depicts graphically the serum albumin, globulin, cholinesterase, and bilirubin levels in a patient with intermittent common duct obstruction from common duct stones. This patient had suffered an intracapsular fracture of the hip in September, 1951, which was treated by extra-articular fixation with two screws. She returned to the hospital in February, 1952, with jaundice and a very low serum cholinesterase level. The jaundice rapidly cleared, however, and cholinesterase and albumin levels rose. She was dismissed from the hospital on March 17. She was seen in the clinic on May 4, with further evidence of improvement in liver function. However, she returned on June 16 with a history of chills and fever and at this time showed a recurrence of jaundice, and an even lower serum cholinesterase level, it having fallen to 0.69 units on this date. She was prepared for surgery with blood transfusions, high-protein, low-fat diet, and vitamin therapy. Cholecystectomy and choledochostomy

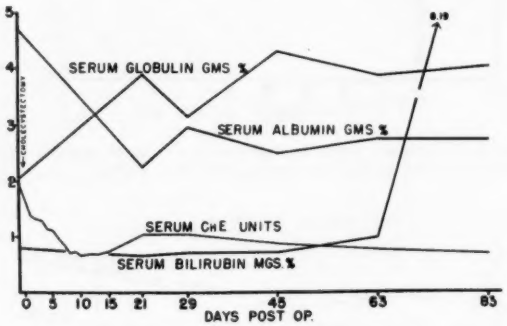
SERUM GLOBULIN GMS %
SERUM ALBUMIN GMS %
SERUM ChE UNITS
SERUM BILIRUBIN MGS %
CHOLECYSTECTOMY
0 5 10 15 21 29 45 63 85
DAYS POST OP.

Chart 8.—Serum albumin, globulin, cholinesterase, and bilirubin levels in Patient O. C., man, aged 66, with acute cholecystitis, cirrhosis of the liver, and carcinoma of the liver.

were performed on July 2. The gall bladder was shrunken, thick-walled, and contained no stones. The common duct was greatly dilated and contained three faceted stones, many small round stones, and sand. A nasogastric tube was placed on the first postoperative day but was left down for less than 12 hours. She was up in a chair on the first postoperative day and took a liquid diet orally on the second postoperative day. A cholangiogram on the sixth postoperative day showed lipiodol entering the duodenum freely. The common duct was still somewhat dilated but showed no evidence of stones. The T-tube was removed from the common duct on the seventh postoperative day. The cholinesterase did not show any great drop with surgery but rose very slowly after surgery. One month after surgery it was 1.42 units, two months following surgery 1.68 units, and four and one-half months following surgery 1.74 units. By this time both serum albumin and globulin had reached high normal levels.

Chart 8 portrays data on a patient who was admitted to the hospital about 12 hours after the onset of an acute attack of upper abdominal pain. There was increasing tenderness and rigidity in the right upper quadrant of the abdomen and evidence

of an enlarged liver. Twenty-four hours after admission a cholecystectomy was done. The gall bladder was found to be acutely inflamed, edematous, distended, stone-containing, and blocked by a stone in the cystic duct. The common duct was not dilated. The liver was greatly increased in size, very hard, and scarred throughout. There were no large nodules. The process appeared to be diffuse and did not have any of the appearance of cancer. All the vessels in the portal system were extremely dilated and bled easily. Portal hypertension was obviously present. A biopsy specimen of the liver showed a large increase in fibrous connective tissue in the periportal spaces, with proliferation of the bile duct. The section was regarded as typical of an early periportal cirrhosis. There was a small amount of fluid present in the peritoneal cavity at the time of operation. On the fifth postoperative day a wound dehiscence developed. The serum cholinesterase level continued to fall until the 10th postoperative day, when it was 0.68 units. First evidence of recovery was seen on the 15th postoperative day, and on the 21st postoperative day the serum cholinesterase level was 1.08 units. Ascites developed, and paracentesis was required on the 18th postoperative day. In the first month following operation it was

Serum Cholinesterase Levels; Biliary Tract Surgery

	Preoperative Level		Postoperative Level*	
	No. of Cases	ChE, Units	No. of Cases	ChE, Units
Choledochostomy				
I. Stones found	16	1.87	16	1.33
II. No stones	20	2.16	18	1.60
Cholecystectomy				
Cholecystitis				
III. Acute and subacute	14	2.15	11	1.54
IV. Chronic with stones	24	2.27	20	1.71
V. Chronic without stones	17	2.25	13	1.89
VI. Chronic with complicating disease	6	2.10	8	1.25

* Lowest in the postoperative period.

thought there was some evidence of decrease in the size of the liver. However, this man died 83 days following surgery. Just prior to his death, jaundice developed for the first time, with the serum bilirubin rising to 8.19 mg. per 100 ml. The serum cholinesterase level had fallen to 0.7 units. At autopsy he was found to have, in addition to cirrhosis of the liver, carcinoma of the liver.

The Table gives data on the average lowest serum cholinesterase levels in the six different groups of patients with biliary-tract surgery. The data include the 49 patients reported on here and the 53 from the preliminary report. It may be seen at a glance that the serum cholinesterase levels tended to vary with the extent of the disease and the surgery performed.

SUMMARY

Studies on 49 patients undergoing biliary-tract surgery emphasized our conclusion in a previous report that serum cholinesterase activity is a valuable index of liver function.

Studies made in the preoperative and in the first 10 postoperative days on these 49 patients showed that the maximum depression of serum cholinesterase activity usually occurred on the third and fourth days following surgery.

The fall in serum cholinesterase activity was much greater in those patients in whom a nasogastric tube was employed.

Any complication delaying oral intake of food led to added depression of serum cholinesterase activity.

In the uncomplicated case with cholecystectomy in which oral intake was resumed shortly following surgery, the serum cholinesterase activity approached normal by the 10th postoperative day.

Those patients having choledochostomy in addition to cholecystectomy were slower in regaining normal serum cholinesterase activity than those having cholecystectomy alone.

In those patients who underwent choledochostomy in whom stones were found and removed, the postoperative depression of cholinesterase was less than in those in whom choledochostomy was performed and in whom no common duct stones were present.

In one patient with prolonged intermittent common duct obstruction the serum cholinesterase activity fell to a very low level and gradually increased over a period of many months following removal of stones from and drainage of the common duct.

In one patient with acute cholecystitis, cirrhosis of the liver, and carcinoma of the liver complicated by wound dehiscence on the fifth postoperative day, serum cholinesterase activity fell to a very low level, increased only slightly three and four weeks following operation, and then gradually fell again up to the time of death, 83 days after surgery.

Serum cholinesterase levels tended to vary with the extent of the disease and the surgery performed.

DISCUSSION

ON PAPERS BY DRS. CHILDS AND PREVEDEL AND DRS. HOWARD E. AND CECIL D. SNYDER AND MISS BUNCH

DR. JOEL W. BAKER, Seattle: I should like to confine my remarks to the very interesting analysis given by Dr. Childs.

In 1950, in an effort to answer the question of how often one should explore the common duct at the time of cholecystectomy, not to overlook common duct stones, we analyzed 500 cholecystectomies. Of these, in 200, or 40%, we openly explored the common duct, and in 76, or 20%, stones were found. I should add that in these positive ducts we did not include 1 mm. pigment debris or 12 instances of fibrotic stricture of the sphincter of Oddi, as adjudged by increased resistance to the 3 mm. probe.

The point of significance was that of the 76 common ducts found to harbor stones, only 4 failed to show pathologic dilatation of 1 cm. or more diameter—and in these 4 we suspected that by operative manipulation we may have forced the small stones from the gall bladder into the common duct.

We wonder therefore if a stone can long reside in the common duct without creating, by obstruction or ballotement, a dilatation of this duct, and, as a corollary to this, whether in the over-all picture one might not resolve the indications for common duct exploration into one indication, that is, the demonstrated dilatation of the common duct, reinforced, of course, by the presence of the other indications. However, if one places so much importance on the size of the duct, one should probably measure it by placing graduated dilators beside the exposed duct for accuracy.

In this application of the principle of dilatation as a guide to the open exploration of the duct, it is reassuring that in our series in 52 patients explored because of jaundice (past or present), and in 4 patients explored for relapsing pancreatitis, and in 2 with acute pancreatitis, the common duct was dilated and would have been explored even if these more recognized indications had not been appreciated.

The advantage of emphasizing dilatation as a chief indication for exploration is not one of simplification alone, but by teaching this principle we may be able to prevent exploratory injury of the common duct. We are convinced that exploration of the dilated duct by competent surgeons will not result in stricture, whereas exploration of the smaller duct could.

Probably one of the practicable uses of the operative cholangiogram as a substitute for open exploration will prove to be in those cases of moderately dilated ducts which are associated with stones impacted and obstructing the cystic duct and in which one suspects therefore that the dilatation of the common duct is compensatory to the physiological loss of the gall bladder rather than to actual stones in the common duct. Herein lies the greatest source for fruitless exploration of the duct, and in such instances an immediate x-ray on the operating table may obviate unnecessary choledochotomy.

Dr. Robert Zollinger, Columbus, Ohio: Dr. Childs certainly emphasized a very important thing. We have been interested, as have Dr. Baker and many others of you, in the recovery incidence in cases of the common duct stone, and especially with relation to jaundice.

(Slide) In about 460 consecutive operations on the gall bladder, we found that it was necessary to explore the common duct in half of the cases. You will observe here that 2 patients in 5, or 40 in 100, were jaundiced at operation. Twenty were jaundiced some time in the past, and the significant fact is that 40% had never been jaundiced at any time. Therefore the surgeon must depend upon his findings at the time of operation, the most important being a dilated common duct. In our experience the normal-sized common duct will not yield a stone in many more instances than 1 in 10.

(Slide) Our incidence of exploration of the common duct has been about 51%, and our recovery rate of common duct stones has been about 21% per 100 patients operated upon. This is consistent with the autopsy statistics pointed out years ago by Crump, wherein it was found that one patient out of five having gallstones will have a stone in the common duct. I think we as surgeons are all interested in improving the end-results of our biliary-tract surgery so that we can restore the confidence of our patients, and many physicians think that this is a good procedure.

Dr. Samuel B. Childs, Denver: Regrettably I do not have any conclusions. I should certainly like to thank Drs. Baker and Zollinger for their discussion of this paper.

The problem that bothers us is this: Of the 100 ducts that we explored for indications, why did we find stones in only half of them? Perhaps Dr. Snyder's serum cholinesterase test will be of some help to us. Perhaps performing a biopsy on the liver in cases in which we have indications for exploring the duct, and not finding stones, may be of help to us.

Dr. Howard E. Snyder, Winfield, Kan.: I should like to point out that in our series of 49 cases there were 20 common ducts explored, and stones were found in 7.

Opening the common duct does carry some insult to the liver. In a previous report on cholinesterase studies we have shown that the fall in cholinesterase activity in the blood serum following biliary-tract surgery is greater than that following surgery upon the stomach, which might be considered a more extensive surgical procedure.

Certainly common ducts must be explored. Perhaps our 40% is low, and we should be opening a few more. However, I think it is important to delineate the indications for opening the common duct because certainly exploration of the common duct does add something to morbidity.

TREATMENT OF COMPLICATIONS OF PLANTAR WARTS

DAVID W. ROBINSON, M.D.
KANSAS CITY, KAN.

THE LOWLY plantar wart, although a very small lesion, may cause great disability. Most plantar warts respond well to simple forms of treatment, but a multiplicity of methods of therapy indicates no single better mode. Electrocoagulation,[1] chemicals,[2] freezing,[3] podophyllin,[4] and irradiation [5] have all produced some good results. Claims of "cures" as high as 95% are made for various treatments, but little is written about the poor results of specific types of therapy. Surgical excision has few advocates because of the resultant painful scars and calluses. Many persons are insensitive to radiotherapy,[6] and the many poor results of such repeated or overenthusiastic treatment are seen by every service for reconstructive surgery.[7] In general, repeated treatments have caused deep fibrosis, which is the fundamental pathologic cause of intractable ulceration with its attendant pain. Crippling orthopedic imbalances of years' standing attest the pain and psychological disturbances with lowered pain threshold commonly seen after years of suffering.

The long-treated painful ulcer surrounded by thick callus, whether or not the wart is any longer active, is bloodless, and further local treatment is not only of no avail but is wrong because it makes the fundamental process worse by adding scar on scar. Good durable coverage with protective qualities and adequate sensation is what is needed. If the area of fibrosis is localized and small, simple excision and closure [8] may be sufficient. Plantar skin will not stretch, because of its dense inelas-

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From the Department of Surgery, University of Kansas Medical Center.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

1. Karp, F. L.: Electrosurgical Removal of Plantar Warts (Loop Treatment), Arch. Dermat. & Syph. **53**:496-497 (May) 1946.

2. Blank, H.: Treatment of Plantar Warts, Arch. Dermat. & Syph. **56**:459-461 (Oct.) 1947. Montgomery, A. H., and Montgomery, R. M.: Mosaic Type of Plantar Wart: Its Characteristics and Treatment, Arch. Dermat. & Syph. **57**:397-399 (March) 1948.

3. Wright, W. L.: Plantar Wart Therapy, U. S. Nav. M. Bull. **49**:707-709 (July-Aug.) 1949.

4. Kurtin, A., and Yontef, R.: Podophyllum Therapy for Plantar Warts, Arch. Dermat. & Syph. **57**:395-396 (March) 1948.

5. Tobias, N.: The Plantar Wart, Mississippi Valley M. J. **70**:206-209 (Nov.) 1948.

6. McLaughlin, C. R.: Plantar Warts: A Plea for Rational Treatment, Lancet **1**:168-169 (Jan. 31) 1948.

7. McIndoe, A. H.; Forbes, R., and Windeyer, B. W.: Symposium: Radiation Necrosis, Brit. J. Radiol. **20**:269-278 (July) 1947.

8. Blair, V. P.; Brown, J. B., and Byars, L. T.: Plantar Warts, Flaps, and Grafts, J. A. M. A. **108**:24-27 (Jan. 2) 1937.

tic dermis and its deep fascial attachment. The avascular defect is usually too great for local closure, and some other more difficult procedure is necessary.

Plantar skin and its protective pad are unique in the body. These tissues are designed to bear weight. Any substitution can never perform this function as well. Split-skin grafts to plantar surfaces in general are too thin and must always be cared for and protected. The thicker the graft with good dermal pad, the more the protection, but normal sensation does not develop in the transplanted skin, and the

Fig. 1.—Full-thickness skin graft in the plantar skin over the head of the first metatarsal of a 9-year-old girl, one year after it was applied. There is no surrounding callus, and good sensation is present in the graft. The wart had not been previously treated and has not recurred. No special protection was used after the first three months.

Fig. 2.—Full-thickness skin grafts in weight-bearing areas of balls of feet, one year after removal of multiply-treated warts which had crippled this 35-year-old woman for many years. The grafts give good coverage, which requires only the wearing of sponge rubber pads for protection. Some tender callus surrounds the juncture of graft and plantar skin, but no recurrence of the warts has been noted.

lack of it may allow damage from weight-bearing to the extent of dangerous vesiculation and necrosis without the patient's knowledge except by observation. Full-thickness skin grafts in weight-bearing areas are adequate coverage for some patients if the fat pad beneath is thick and vascular (Figs. 1 and 2). Especial care must be taken of these grafts early before any sensation has returned.

Pedicle coverage is usually needed if the underlying bed of the plantar defect is avascular, if the area overlies a bony prominence, or if the defect is much larger than 1 cm. in diameter. Wide excision is necessary to remove all scar. Sometimes part of the aponeurosis must be excised, exposing tendons or heads of metatarsals. Occasionally bony prominences, as in decubitus ulcer surgery, must be removed. Sesamoid bones, especially over the head of the first metacarpal, may be the underlying cause of pressure points and must be removed. Osteoradionecrosis of meta-

Fig. 3.—Osteoradionecrosis of metatarsal head and shaft from repeated extensive radiotherapy. The great toe had been previously removed for the same reason. A large avascular ulcer in the ball of the foot required a direct cross-leg flap for coverage, performed without a delaying procedure. The lesion caused this 50-year-old aircraft worker to quit work, but the repair allowed him to return to his old job within four months of the reconstructive procedure.

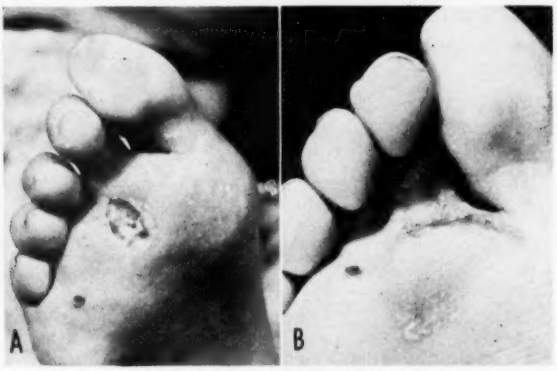

Fig. 4.—*A*, ulcer over metatarsal heads of 21-year-old woman two years after roentgen therapy. Severe pain had produced some orthopedic imbalance from walking abnormally, and some psychic disturbance had developed. *B*, plantar surface four months after local rotation flap from beneath the bases of the toes. The donor bed of the flap was covered with a full-thickness skin graft. The patient is walking without pain and has unlimited activity although she wears a protective pad in her shoe.

tarsal heads necessitates removal of these bony parts (Fig. 3). Whenever possible, local flap shifts [8] are better than distant pedicle coverage. Most often, a flap can be rotated from beneath the toes, from over the instep, or from the side of the foot (see Fig. 4). The donor defect can be covered by a thick split- or a full-thickness skin graft. The flap should be planned so as not to expose further bony prominences

which would be inadequately covered by a free skin graft and so as to section as little as possible of the normal nerve supply to the pedicle. Farmer (in discussion on Dickson [9]) advocated shifting as a large rotation flap the entire soft tissue of the half of the foot, freed from the aponeurosis and cut from beneath the toes.

A useful local flap, when the defect is over the ball of the foot, relatively near the bases of the four small toes, is the filleted toe flap.[10] The loss of the external toe causes very little disability, and the covering flap from the deboned toe, carrying its nerve and blood supply, makes excellent coverage (Fig. 5). Ulcers at the base of the great toe are not suitable for this treatment, as the balancing factor of this toe is too important to allow it to be sacrificed.

Distant pedicle grafts are usually cross-leg flaps.[11] This procedure should be reserved for the most severe cases, in which the surface loss on a weight-bearing area is large and cannot be covered by local flaps without distortion and local tension on the suture line (Fig. 6). Flaps should be so designed and executed as to be shifted without jeopardizing the blood supply and to fall in place with no tension on the suture line. A few deep sutures of fine chromic absorbable surgical suture

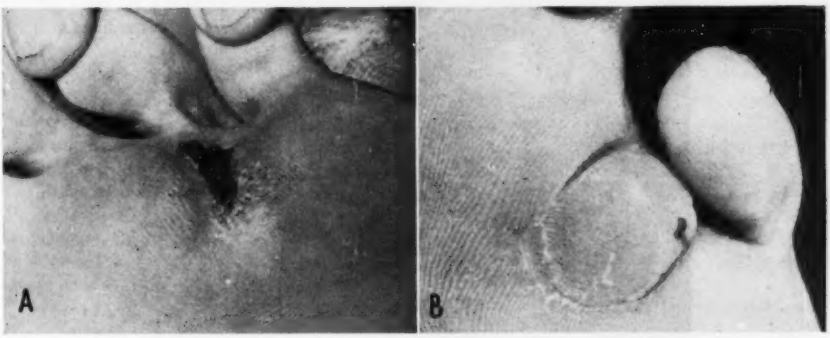

Fig. 5.—*A*, ulcer over head of fourth metatarsal four years after multiple roentgen therapy was given to patient, a 25-year-old soldier. The pain was disabling enough to preclude active duty. *B*, filleted toe flap gives good coverage with full sensation. This single operation will allow weight-bearing and nearly complete activity within one month. The procedure here was performed three years before, and no disability has been present since then.

approximate fascia and dermis accurately enough that only a few fine steel wire skin sutures at wide intervals are necessary. Very little skin reaction from sutures will be present.

Orthopedic surgeons have been more prone to utilize the "pie" operation of Dickson.[9] This procedure is more radical than the coverage operation described herein, with the exception of the cross-leg flap. The operation is designed to elim-

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11. Shaw, M. H.: Treatment of Chronic Ulceration After Irradiation of Plantar Wart, Brit. M. J. **1**:11 (Jan. 3) 1948. Ghormley, R. K., and Lipscomb, P. R.: The Use of Untubed Pedicle Grafts in the Repair of Deep Defects of Foot and Ankle: Technique and Results, J. Bone & Joint Surg. **26**:483-488 (July) 1944. Haggart, G. E.: The Conservative and Surgical Treatment of Plantar Warts, S. Clin. North America **14**:1211-1218 (Oct.) 1934.

inate the scarred ulcerated area on the sole by elliptical excision and longitudinal closure. It removes the underlying bony prominence of the metatarsal head by removing the entire metatarsal beneath the ulcer and the attached toe distal to the defect. The foot is collapsed and narrowed by sutures. This operation has not been performed by our service but has only been observed. The fundamentals of remov-

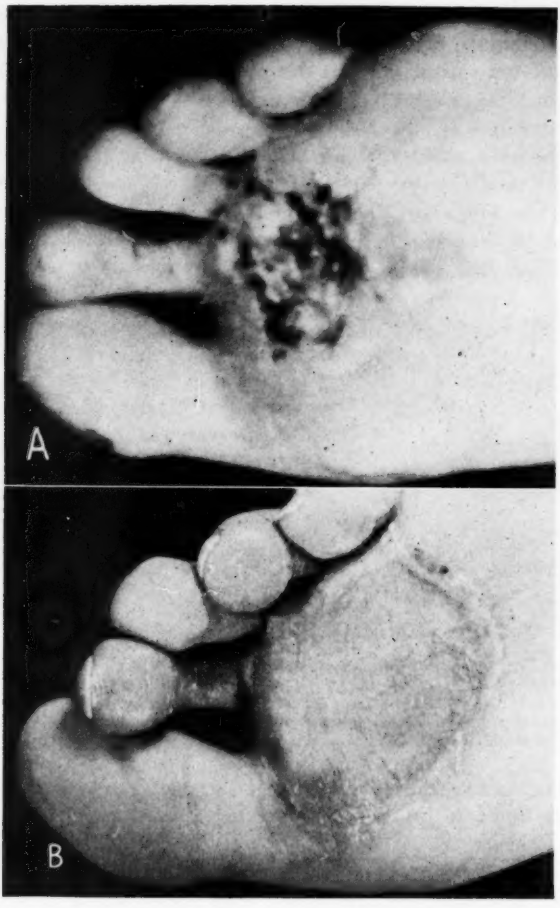


Fig. 6.—*A*, Large painful ulcer of the ball of the foot of a 15-year-old boy whose plantar wart had been treated by roentgen therapy four months before. *B*, plantar surface with pedicle flap coverage giving completely usable foot. The cross-leg flap operation had been performed two years before without a delaying procedure. Sensation had returned within six months and unlimited activity without protection has been allowed since one year after surgery.

ing all scar and the underlying pressure point are adhered to, but the principle of making long scars against the cleavage lines on the plantar skin is violated, and, furthermore, the arch is depressed so that new pressure points are produced. This operation is indicated if coverage procedures are unwarranted or too difficult from the technical or economic standpoint.

Postoperative care is important. Weight-bearing should not be allowed before three weeks, and then only with full protection by sponge rubber pads, felt, and arch supports. The dependent position of skin grafts is not allowed for two weeks. Mechanical support with ace® bandages or elastoplast is insisted upon for at least two months. Before weight-bearing is allowed, canes and crutches should be used, and protective pads, metatarsal bars, or special shoe arrangements should be prescribed by an orthopedic consultant. This advice is necessary, and the need for it is explained to the patient before surgery is undertaken. Calluses may develop at suture lines of grafts or flaps and can be kept soft and trimmed, but the scar producing the callus may have to be excised and closed. It should be remembered that the fundamental cause of the wart may not have been removed or be removable and a new wart may start. The many years of orthopedic imbalance from walking in an unusual manner to avoid pain may produce a crippled foot that is not correctable.

DISCUSSION

DR. LOUIS T. BYARS, St. Louis: The plantar wart is the equivalent of any localized benign skin tumor. It causes serious discomfort because of its position; it is sensitive to radiation occasionally but not always. It is curable by adequate excision. There is no mystery involved. A comfortable surgical repair can normally be made.

Widespread clusters of stubbornly persistent warts on the sole are not the usual situation but do occur.

Inability to plan a proper repair leads to an incomplete excision. The simplest repair is not always best. Simple suture of a defect is not adequate except for the smallest lesion. Adequate excision of the wart with simple suture of the defect under tension will produce a keratotic painful scar over a pressure point.

Free full-thickness skin grafts are usually satisfactory if underlying subcutaneous padding is present. The scar border of the graft should be placed away from a pressure point. Subcutaneous padding must be provided over pressure points through the shifting of local flaps if it is deficient. The cross-leg flap is used only when other methods have been considered and rejected for good cause.

Proper protection during the "seasoning" period of the repair is essential, and the patient can well afford this time when its cost is balanced against a lifetime of pain and annoyance.

These warts are not easily "frightened" away, as are the warts of childhood, and it is the continued unsuccessful trial of inadequate measures which promotes a feeling of hopelessness and causes the patient to lead a needlessly painful existence.

Radiation should not be continued when its lack of efficacy is proved. If the wart does not prove sensitive when first properly exposed, radiation must be abandoned. A high percentage of patients have radiation damage and the wart is still present.

INTERCOSTAL DISSECTION AND RADICAL MASTECTOMY

WILLIAM B. HUTCHINSON, M.D.
SEATTLE

THE STATISTICAL evidence that the early diagnosis and treatment of cancer and curability are not necessarily synonymous would make one wonder if we might not be further ahead to discard many of our present ideas about cancer. This might well be applied to the problem of treatment of carcinoma of the female breast. Particularly is this so when we realize that there has been little or no real progress in the management of this condition during the past 65 years since Halsted devised his surgical procedure of radical mastectomy. Further emphasis on the need of a more careful appraisal of our past and present accomplishments has been appearing with increasing incidence in the current literature. With these thoughts in mind it seems timely for surgeons, particularly those with accumulated experience, to view their accomplishments and failures critically from the following standpoints. First, how has the past and present surgical treatment of carcinoma of the breast affected the natural history of the disease? Second, what have been the underlying principles that justify our methods of treatment? Third, how might we alter our treatment in the best interest of the patient?

Pathological, clinical, and statistical observations have shown that the biological behavior of cancers of the breast has very little correlation with the so-called early lesion, the location, size, and duration of the tumor, and the clinical symptoms. Haagensen and Stout [1] found involvement of axillary lymph nodes in 50% of cases with a clinical history under one month's duration, and MacDonald [2] found this involvement in 59%. In my series here reported the incidence was 42%. Daland [3] reported a 22% five-year survival in 100 patients with untreated carcinomas of the breast; 5% of the patients were alive in 10 years. The several modes of tumor spread have to a large extent been overlooked because of an overemphasis on lymphatic spread. This has been based on the frequent misconception that the lymphatic system is an autonomous circulatory system until it reaches communication with the major blood vessels. We often forget that the blood and lymphatic systems at the point of tissue-fluid movements are closely related. No doubt herein lies the explanation of the all too frequent case with a small early lesion, negative lymph

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

1. Haagensen, C. D., and Stout, A. P.: Carcinoma of the Breast: Results of Treatment, Ann. Surg. **116**:801-815 (Dec.) 1942.

2. MacDonald, I.: Biological Predeterminism in Human Cancer, Surg., Gynec. & Obst. **92**:443-452 (April) 1951.

3. Daland, E. M.: Untreated Cancer of the Breast, Surg., Gynec. & Obst. **44**:264-268 (Feb.) 1927.

nodes, and widespread blood-borne metastasis. This survey shows that much time and energy were expended in the radical treatment of lesions predestined at the time to be lethal.

In 1947 Handley with Thackray [4] reported five cases in which intercostal nodes were dissected out for pathological analysis. It was this report that furnished the stimulus for the present three-year study beginning in 1949 and including the years 1949, 1950, 1951, and representing 81 consecutive cases of carcinoma of the breast. The case material for this study is from my private practice. The only basis of selection was the generally accepted criterion of operability for carcinoma of the breast. In the 81 cases under consideration the procedure has been the excision and frozen section of the primary breast tumor to establish the diagnosis. The removal and section of any questionable supraclavicular lymph nodes were done on a very few occasions. In the absence of supraclavicular metastasis, a routine Halsted radical mastectomy was done in each case and was followed by an exploration of the first three interspaces. This was accomplished by severing the intercostal muscles from the costochondral junction with the sternum. The pleura and the internal mammary vessels were thus exposed. They were then stripped of any lymph nodes or fatty tissue. Often the fatty tissue contains unsuspected aggregations of lymphoid follicles. No attempt was made to do anything more than investigate the interspace areas, and this is not to be regarded as a method of attack upon internal mammary spread. The investigation is designed to give information concerning the dissemination of carcinoma of the breast in the lymphatic system, outside of that portion in the time-honored axilla. In no instance was the exploration injurious to the patient, and it added only 15 to 20 minutes to the procedure.

All the material was subjected to careful gross and histological study in the pathological laboratory of the Swedish Hospital by Dr. Paul K. Lund. All lymph nodes in all specimens, from both the axilla and the intercostal spaces, were studied, and the results were tabulated. In addition, many sections were made through the fatty tissue from the interspaces in a search for unsuspected lymphoid collections. On a few occasions two technical errors were made. First, the internal mammary vessels were slightly torn or severed. This can easily be corrected in the same interspace, or in the one above or below, depending on which vessel is injured. Second, the pleura was entered. This is ordinarily a very small tear, and since it has been anticipated it is of no great consequence. We use an intratracheal tube so the anesthetist can apply positive pressure at any time. I have made it a point to examine the lung just before closing the skin in order to make certain the lung is out against the pleura. Any small tear inadvertently made will allow air to enter the pleural space and may cause the lung to collapse. The opening should be maintained for the air to escape as the lung is reexpanded before it is sewed shut.

I do a radical mastectomy for carcinoma of the breast for two reasons. The first, and possibly the only good reason, is to reduce the incidence of local recurrence. Halsted [5] devised the procedure with this thought foremost in his mind. Nothing better has ever been devised for adequate removal of breast and axillary contents.

4. Handley, R. S., and Thackray, A. C.: Invasion of the Internal Mammary Lymph Glands in Carcinoma of the Breast, Brit. J. Cancer **1**:15-20 (March) 1947.

5. Halsted, W. S.: The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894, Ann. Surg. **20**:497-555, 1894.

The great surgeons of the late 1800's had an appalling incidence of recurrence in the skin. Even Halsted's results, which were infinitely better than most and which showed a 6% local recurrence, were found in the course of time, as Lewis and Rienhoff [6] noted in 1931 when reviewing his original 50 cases, not to be as satisfactory as they were thought to be at first. As observation time increased a 32% local recurrence rate was noted. Second, it is conceivable that the radical operation will reduce the secondary metastatic spread from the axillary lymphatics in those patients in whom metastatic disease is found primarily in the axilla.

Handley and Thackray [7] point out that far too much attention has been given to the axillary avenue of spread, and far too little to the spread along the internal mammary vessels. The spread here is inside the bony thorax, where it is close to vital structures and safe from the radical mastectomist. Knowledge of this area of spread is not new and was appreciated in the early nineteenth century. At the turn of the century Halsted wrote of exploring this area, but apparently did not do so. Sampson Handley in 1922 explored the mediastinum in six cases and found invaded nodes in two. He suggested the routine use of radium in the intercostal spaces as a therapeutic measure. Perhaps the lack of work here was due to the

TABLE 1.—*Occurrence of Metastatic Disease* *

	Metastatic Disease		Percentage of Metastatic Disease
	No.	%	
Positive axillary nodes	41	50	95
Positive intercostal nodes	21	26	48
Positive axillary and positive intercostal nodes	19	23	44
Positive axillary and negative intercostal nodes	22	27	51
Negative axillary and positive intercostal nodes	2	2.5	5

* Total no. of cases 81; total with metastatic disease 43, or 53%.

fear of pneumothorax and the inability of the anesthetist and the surgeon to cope with it as they can so easily do today.

In evaluating the 81 cases reported here we find metastatic disease occurred in 43, or 53%. In 41, or 50%, it occurred in the axilla. Of greater prognostic significance is the finding of internal mammary spread in 19 of these 41. This would seem to have negated any curative value of the radical mastectomy done in almost one-half of these 41 cases. In 21, or 26%, the metastasis occurred in the intercostal nodes. Only two patients failed to show other metastatic foci in the axilla. Twenty-six per cent, or one-fourth, of the persons upon whom I operated were exposed to a perfectly useless procedure, while fatal metastatic disease had been disseminated more widely than had hitherto been realized.

If the work of Saphir and Amromin [8] is taken into consideration, this figure would be one-third higher. On examination of serial sections of all the axillary

6. Lewis, D., and Rienhoff, W. F., Jr.: A Study of the Results of Operations for the Cure of Cancer of the Breast Performed at Johns Hopkins Hospital from 1889 to 1931, Ann. Surg. **95**:336-400 (March) 1932.

7. Handley, R. S., and Thackray, A. C.: The Internal Mammary Lymph Chain in Carcinoma of the Breast: Study of 50 Cases, Lancet **2**:276-278 (Aug. 13) 1949.

8. Saphir, O., and Amromin, G. D.: Obscure Axillary Lymph-Node Metastasis in Carcinoma of the Breast, Cancer **1**:238-241 (July) 1948.

nodes from 30 patients with carcinoma of the breast, who on previous routine examination had shown freedom from axillary nodal invasion, they found tumor cells in one or more nodes in 10 patients (33.3%). These facts make us aware that the number of cases in which the carcinoma is confined to the breast proper is small at the time of operation.

It is of interest to note that in the present series there were fewer lesions proportionately that occurred in the inner half of the breast than were reported by Handley [7] in 1949. In my series there were many more lesions proportionately in the outer half that showed intercostal nodal spread. This leads me to believe that it really makes very little difference where the lesion is; if it has a spreading potential, it spreads. Of those intercostal nodes in patients with a history of duration of the breast tumor of one month or less, 15% were positive. I would, therefore, disagree with Urban [9] in treating only inner-half lesions with en bloc internal mammary

TABLE 2.—*Lymph Involvement*

	Site of Primary Growth					
	Inner Half		Outer Half		Total	
Total cases	20*	17†	61*	33†	81*	50†
All lymph nodes free from growth	14	4	26	12	40	16
Internal mammary nodes alone involved	1	2	1	1	2	3
Axillary nodes alone involved	5	1	36	14	41	15
Both axillary and internal mammary nodes involved	3	10	16	6	19	16

* Hutchinson's figures in this column.
† Handley's figures in this column.

TABLE 3.—*Duration of Lesion*

	Less Than 1 Month	1-6 Months	6 Months+
Positive axillary nodes	14 (42%)	12	15
Positive intercostal nodes	5 (15%)	6	10
Negative axillary nodes	19	11	10
Negative intercostal nodes	28	16	16

dissection. If subsequent follow-up shows the procedure to be of any value whatever in the over-all reduction of mortality statistics, it would seem only rational to use it in all breast carcinomas, as the region of spread of a given tumor is unknown.

The ratio of the number of axillary lymph nodes with metastases to the total number of axillary lymph nodes bears no significant relation to the probability of internal mammary spread. All patients in whom internal mammary spread was encountered at surgery, and who had radical mastectomies three years ago are now dead. Only 2 of 12 patients operated on two and one years ago remain without signs of residual disease to date. Fifty per cent of those already dead of generalized disease or those alive with generalized disease have shown evidence of local recurrence. Thus, of 18 patients with internal mammary spread, 9 are already dead while 7 are alive with their disease. These findings, among others, indicate the

9. Urban, J. A., and Baker, H. W.: Radical Mastectomy in Continuity with En Bloc Resection of the Internal Mammary Lymph-Node Chain: A New Procedure for Primary Operable Cancer of the Breast, Cancer **5**:992-1008 (Sept.) 1952.

futility of radical mastectomy as a curative procedure in cancer of the breast in which spread to the internal mammary lymphatics has already occurred.

How, then, can these facts be of practical significance in the treatment of carcinoma of the breast? Do the internal mammary lymphatics constitute another lymphatic area that should be included in our routine operative procedure? Reducing the problem to its simplest terms, we have one of two paths to follow. First, we may extend our surgical scope to include axilla, supraclavicular and retroclavicular structures, en bloc dissection of the internal mammary chain, and anterior mediastinal structures. If it is logical to believe that surgery is the answer, then it should be all-inclusive. The inability of the surgeon to completely rid any single one of these localities of all their lymphatics and lymph nodes is obvious to us all. This is without any consideration of the blood-borne or perineural spread. If in the

TABLE 4.—*Relation of Intercostal Nodes to Percentage of Positive Axillary Nodes*

	Percentage Involvement of Axillary Nodes			
	None	Less Than 25%	25%-75%	75%-100%
Number of positive intercostal nodes	2	8	2	9
Alive and well	1	2	1	1
Alive with disease	1	3	0	3
Dead	..	3	1	5

Ratio of frequency of interspace involvement: No. 1—11; No. 2—8; No. 3—2

TABLE 5.—*Positive Intercostal Nodes*

Condition of Patient	3 Years	2 Years	12 Months	6 Months
Alive and well	0	1	1	3
Alive with disease	0	3	4	..
General metastasis	..	(3)	(4)	..
Local recurrence and g. m.	..	(1)	(2)	..
Dead	6	2	1	..
General metastasis	(3)	(2)	(1)	..
Local recurrence and g. m.	(3)	(1)	...	..

course of time this procedure fails, more extensive procedures must then be devised if this reasoning is to be carried to its logical conclusion. Even now the law of diminishing returns presents itself for our evaluation. This estimate must also consider the worth of dying of uncured treated carcinoma.

Second, we may decide that if the cancer can be proved by biopsy or frozen section of lymph nodes at the time of initial surgery to have extended to the supraclavicular or internal mammary nodes, then it is predestined to be surgically incurable. Many cancers will have reached a stage of autonomy.[10] Perhaps it might be preferable to do a simple mastectomy in patients with positive nodes in these areas. A routine diagnostic breast biopsy is done first. If the results are positive, the interspaces are then explored. Further procedure depends on the findings, because if they are negative a radical mastectomy is done, but if positive a simple mastectomy would be the operation of choice. Based on the findings upon comple-

10. Green, H. S. N., and Lund, P. K.: The Heterologous Transplantation of Human Cancers, Cancer Res. **4**:352-363 (June) 1944.

tion of this survey, this has since been my method of management. The errors of execution are due to the fact that the intercostal lymph nodes are comparatively very small. Freezing these nodes is often difficult, but any error made will be on the negative side. Thus the routine radical operation, instead of a simple mastectomy, will be done following the biopsy and exploration of the intercostal nodes. This would have been done if the internal mammary nodes were not explored. After wound healing has occurred, deep x-ray therapy is given to the axilla and to the supraclavicular and internal mammary chain bilaterally, in the hope not of curing, but of delaying the progress of the tumor.

This is not in any sense an indictment of extirpative surgery, but an attempt to align procedure with factual data. Surgical refinements allow operations of continually expanding magnitude, but place on the operator greater responsibility for accomplishment. It is my conviction that the only possible progress beyond its current state that surgery has to offer in dealing with carcinoma of the breast, is to attempt to recognize and eradicate the precancerous breast prior to the development of malignancy. In view of our present concept of precancerous pathological processes, the pathologist and the surgeon working jointly can make great strides in this direction. This in my opinion will accomplish more for the good of a greater number of women than a more radical approach to surgical removal of breast cancer.

BASTING THE AXILLARY FLAP FOR WOUNDS OF RADICAL MASTECTOMY

E. LAWRENCE KEYES, M.D.
BRAY O. HAWK, M.D.
AND
CHARLES S. SHERWIN, M.D.
ST. LOUIS

HALSTED,[1] when closing wounds of radical mastectomy, stitched the axillary flap of skin "by interrupted, buried sutures of very fine silk to the fascia just below the first rib in such a way that the skin partly enveloped the large vessels." Up to 1913, Halsted apparently sutured the axillary skin flap only when grafting skin; since 1949 others [2] have begun to suture the axillary skin flap not only when grafting, but also when not grafting, for reasons which will appear in this paper. It is the axillary flap, rather than the chest flaps, which is most in need of basting, whether skin is grafted or whether it is not grafted, a fact which it took us years to appreciate.

For obtaining uncomplicated healing of mastectomy wounds, suture fixation of the axillary skin flap has proved superior to mechanical pressure in the axilla. Objectives, however, are identical whether suturing is done or whether pressure is applied to skin flaps, as Blair [3] noted in 1924. These objectives are (1) closing dead spaces, (2) preventing ooze beneath flaps, (3) preventing venous and lymph congestion in the flaps themselves, and (4) holding the flaps evenly onto their beds. Theoretically, suturing should surpass pressure in effectiveness, particularly in the axilla, where motion of the arm tends to dislodge flaps and where tension on suture lines tends towards "tenting." Negative pressure can help.[4]

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

This study was from the Department of Surgery, St. Louis University School of Medicine, aided in part by Grant CT 619 of the United States Public Health Service, by the Missouri Division of the American Cancer Society, and by the Missouri State Division of Health.

1. Halsted, W. S.: Developments in Skin-Grafting Operation for Cancer of the Breast, J. A. M. A. **60**:416 (Feb. 8) 1913.

2. (*a*) Byars, L. T.: Personal communication to the author. (*b*) Orr, T. G.: Symposium on Recent Advances in Surgery: Radical Operation and Palliative Therapy for Carcinoma of the Breast, S. Clin. North America **29**:1341 (Oct.) 1949. Orr, T. G., Jr.: An Incision and Method of Wound Closure for Radical Mastectomy, Ann. Surg. **133**:565 (April) 1951. (*c*) Urban, J. A., and Baker, H. W.: Radical Mastectomy in Continuity with En Bloc Resection of the Internal Mammary Lymph-Node Chain, Cancer **5**:992 (Sept.) 1952.

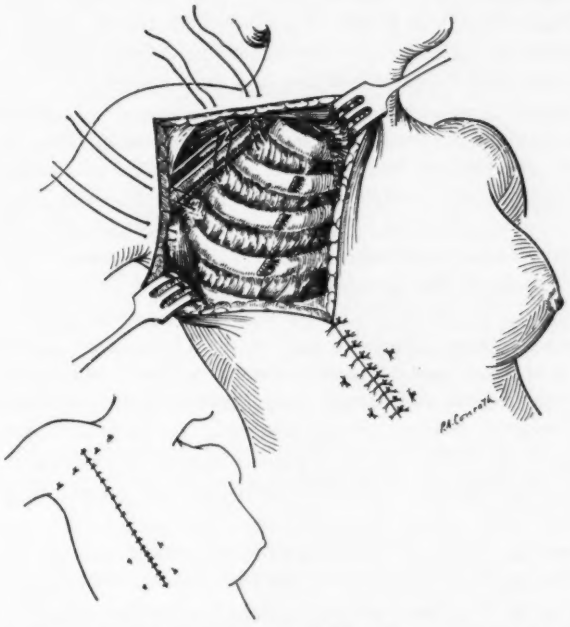
3. Blair, V. P.: The Influence of Mechanical Pressure on Wound Healing, Illinois M. J. **46**:249 (Oct.) 1924.

4. Raffl, A. B.: The Use of Negative Pressure Under Skin Flaps After Radical Mastectomy, A. M. A. Arch. Surg. **136**:1048, 1952.

METHOD OF SUTURING THE AXILLARY FLAP

Halsted, in 1913, and others such as Byars [2a] since, have buried silk or absorbable surgical sutures to suture the axillary flap; still others, such as as Orr,[2b] Urban,[2c] and we ourselves, prefer the basting technic illustrated here.

In basting, four or five sutures of medium skin silk, threaded on large curved stay-suture needles, are inserted parallel to and about 1 cm. below the axillary vein into the first interspace (rather than into the second and third interspaces as shown in the Figure) and into the latissimus dorsi muscle. The axillary flap must be sutured with the arm abducted 90 degrees during closure, and no suture must penetrate the pleura. It is better to use a skin graft than to close the mastectomy wound



The flap is basted high in the axilla parallel to the vein, with the arms abducted 90 degrees; a graft is applied if necessary, with any type of incision. Chest basting is less necessary than axillary basting. Drains are important, though omitted from the illustration.

too tightly, in order to avoid tenting and skin necrosis; and in grafting, the skin flaps on the chest as well as the graft itself are basted, in addition to the basting of the axillary flap. The basting sutures are removed when first the wound is dressed on the fourth to the sixth day postoperatively.

Up to five short Penrose drains are inserted, one over each of the two cut pectoralis muscle tendons, one low in the axilla over the latissimus muscle, one at the highest costochondral junction, and one over the excised upper rectus abdominis fascia; the drains are removed from the fourth to the sixth day postoperatively.

The axillary flap is basted after incisions of all types, and either with or without skin grafting. Chest flaps, if also basted, may obviate grafting.

METHOD OF THIS STUDY

Since 1949, 17 axillary flaps have been basted by one of us (K) in 16 private patients, one of the 17 patients having undergone bilateral radical mastectomy during that time. To evaluate the effectiveness of axillary basting, 17 other successive private patients (K) whose axillae were not basted were selected; some of the latter 17 patients had their chest flaps basted about skin grafts.

Of the 17 patients with basted axillae, 5 had skin grafts; of the 17 patients without basted axillae, 12 had skin grafts. None of the 34 patients died postoperatively.

RESULTS OF BASTING THE AXILLA

Basting diminished the number of patients with grafts from 12 to 5. No postoperative complications arose in the 17 patients with basted axillae. However, of the 17 with nonbasted axillae, an axillary hematoma developed in one; and axillary abscess in another, and a wound infection in a third patient.

Wounds healed more quickly with basting than without basting the axilla, and fewer sloughs developed in the skin on the chest with basting. Thus, wound healing was completed, and the last dressing done, by the second postoperative month in 14 of the 17 patients with basted axillae; whereas healing was completed by the second month in only 10 of the 17 patients with nonbasted axillae. The remaining patients required from three to seven months for complete wound healing.

No massive edema of the extremity developed during the first three postoperative years in any of the 34 patients, whether their axillae were basted or not. Mild, transient edema, however, developed in 6 of the 17 patients with basted axillae, as well as in 4 of the 17 patients with nonbasted axillae. Their hands would swell with some pitting edema and partial disappearance of the veins on the dorsum, requiring the removal of rings for two months at the longest. This edema of the hands occurred always in the same time period; namely, between the second and the sixth month postoperatively. Therefore edema did not appear to be altered by basting of the axilla.

Axillary basting shortened hospitalization for patients; 11 of the 17 patients with axillary basting were discharged the second to the seventh day postoperatively, against only 6 of the 17 patients without axillary basting discharged the fourth to the seventh day postoperatively.

Blood was conserved by basting the axilla. Thus the fourth-day dressing of a woman of 83, after radical mastectomy basted without grafting, showed no blood to have soaked entirely through a thin Dakin pad, the blood having saturated merely three thicknesses of flat dressings next to the wound. By comparison, certain patients without basting of the axilla had seepage through heavier dressings as early as the evening of operation, or by the next morning. What this saving of the patient's own blood means for her nutrition and for wound healing need not be discussed here.

Arm motion was begun when patients awakened. Ultimate motion of the arm was free and without binding scars in all 34 of the patients, whether basting was done or not.

Basting sutures cause pain till removed. Basting adds time to the operation. These are objections to the method.

SUMMARY

This study of 34 patients after radical mastectomy indicated that suture fixation of the axillary flap by basting proved superior to omission of suture fixation of the axillary flap in these respects: basted wounds healed faster and with less sloughing than those without basting of the axillae; fewer complications arose in the basted axillae, and fewer needed grafting. The hospital stay of patients was shortened, while their nutrition was better conserved because the postoperative seepage of their own blood was diminished.

Operations were performed at Jewish, St. John's and Barnes hospitals. The illustration is by Philip A. Conrath.

DISCUSSION

ON PAPERS BY DR. HUTCHINSON AND DRS. KEYES, HAWK, AND SHERWIN

DR. LOUIS T. BYARS, St. Louis: Plastic surgeons have often basted free skin grafts to conform to the irregularities of the recipient area. Obviously, it is necessary for a free skin graft to be in contact with its recipient area if circulation is to be resumed. It is not equally important for the pedicle flap to be accurately in contact with the area to which it is applied because the flap has its own blood supply and will survive without this contact. It is just as important, however, if the healing of the flap is to proceed at the maximum rate and if infection or hematoma formation is to be avoided. This objective can be achieved by properly applied and maintained pressure dressings. All too frequently, however, the pressure dressing does not perform all of its functions, and if the flaps have been basted properly the wound is safeguarded. This technique is of additional benefit if complications do arise. All too frequently, a tunnel is formed into the axilla if skin flaps necrose from lack of blood supply. The presence of this tunnel, which harbors many germs, delays secondary repair. Proper apposition of tissues in the axilla forestalls this delay. The only harm I can see which might arise from employing the basting technique would be the possibility of the mattress suture strangulating a blood vessel and perhaps jeopardizing circulation if it is already deficient. It would appear that basting is a technique which is likely to speed the patient's recovery and reduce the hospital stay. Always drain the axilla.

DR. THOMAS G. ORR, Kansas City, Kan.: For many years I did not realize the importance of suturing flaps. It is very important indeed, and the reasons, I believe, are obvious.

Suturing the flaps down carefully, approximating them to the underlying tissues, as every plastic surgeon knows, minimizes the collection of bloody serum beneath the flaps. That in turn minimizes infection, and also minimizes the formation of scar tissue.

If serum collects beneath the flaps, repeated attempts at aspiration or draining are bound to increase the incidence of infection and to increase fibrosis. That in turn will certainly increase the edema of the arm.

[Slide] Dr. Keyes spoke of Dr. Halsted. This drawing was published in 1913 and shows how Dr. Halsted sutured the flap up beneath the vessels to minimize the collection of serum and to minimize the edema of the arm. I think suturing beneath the vessels is not by any means the whole story.

[Slide] I have perhaps more difficulty with the accumulation of serum out over the arm than I have elsewhere. In suturing the flap down I try to put sutures in the coracobrachialis and sometimes down near the stump of the pectoralis major where it has been divided, as well as in the intercostal spaces. The flaps are drawn up into the axilla as high as possible.

I now suture the latissimus dorsi of the chest wall to eliminate some of the space in that area.

These coaptation sutures may be placed obliquely, as you see, as partial tension sutures to take some of the tension off the suture line.

We have been using this little rubber tubing. I think it was described by Major Chappel, an English surgeon, during World War I. It has been called "Major Chappel's button suture"—not a very good term for it, but it comes in very handy for guarding one's suture material.

[Slide] I use mechanic's waste, as described by Dr. Keyes, leaving the ends of the sutures long, to tie the waste in place.

[Slide] Mechanic's waste is better than marine sponges, I can assure you, for pressure. I have tried both, and the waste is much better. This patient has been operated on recently, and shows the location of the various sutures. You can see that there are some sutures high in the axilla over the coracobrachialis, and one slightly out on the arm to obliterate that dead space.

DR. WILLIS D. GATCH, Indianapolis: I should like to discuss briefly Dr. Hutchinson's paper—a very excellent paper. I think he is quite right in saying that the time has come for a revision of our fundamental theories on the treatment of cancer.

The theory that cancer spreads almost entirely by way of lymphatics was advanced by the work of Halsted and about 60 years ago by Sampson Handley, and has dominated the treatment of cancer in all locations ever since. The idea was that to cure cancer you must eradicate the primary growth and all of its ramifications by cutting everywhere through normal tissue beyond the uttermost limits of the growth.

I wish to speak first about the demonstration of cancerous lymph glands in the axilla. Great prognostic importance has been attached to this. If the axillary fat is examined in the fresh state at the close of the operation, a negative finding will be absolutely worthless because you can't feel the glands.

Dr. Clyde Culbertson, a very conscientious pathologist, who studied specimens removed by me, devised the following method: He fixed the specimens in formaldehyde for 48 hours, put them on a slicing machine, and sliced them in sections 1/8 in. (0.32 cm.) thick. He then examined each one of these with a magnifying glass and took out every suspicious area for microscopic examination. The results were terrible. He found cancerous metastases in almost every breast in which, on gross examination of the fresh tissue, one would think there was none.

If you fix the tissues in formaldehyde for 24 to 48 hours and then palpate them, you can feel the cancerous glands as shot-like nodules in the axilla and you will be startled to discover how many there are.

There seems to be a rather widespread doctrine that if you remove the primary growth and all cancerous lymph glands you will cure cancer. Of course, the lymph glands may contain cancer, but all the fat around them also contains cancer. The lymphatics are full of it, and you have to eradicate all of these along with the lymph glands if you are to cure cancer, on this theory.

I believe that this is anatomically impossible. Halsted himself always had serious doubts about the possibility of removing every particle of cancer-containing fat from the axilla.

Of course, it is true that we cure many patients clinically, but as Lewis and Rienhoff said in 1932, the patient may remain clinically cured for years, but whether the patient is ever cured in the pathologic sense, is open to question. I think Lewis and Rienhoff were correct about that.

I believe that to extend the operation for cancer of the breast into the neck or the chest is not warranted by what we know about its spread. As Dr. Hutchinson said, we know now that cancer of the breast in many cases, possibly in all cases, spreads by the blood vessels. The work of Batson has been very suggestive along that line.

One other point: We have demonstrated that we know very little about the natural history of cancer in the human being. How long it lasts from the time it first appears in one cell or one group of cells until, untreated, it causes death, we do not know. We usually say a patient's life is from three to four years after discovery of the cancer. That, however, varies so much in the individual case that this criterion is practically useless.

One of my untreated patients died within a year from the time she noticed the growth, and another died after 25 years. Six pathologists have done autopsies on groups of men over 50 years of age, who had had no signs of prostatic trouble, and have reported the finding of little undiscovered cancers in from 16 to 46% of cases.

We discovered, in examining apparently normal breasts, several little cancers of microscopic size.

So, I advance the thought that our good results in the treatment of cancer are in great part due to the natural resistance of the body to cancer, and not to what we do in removing every little lymphatic vessel that has cancer. The natural resistance of the body to cancer, which is one of the fundamental facts of nature and which can hold cancer of the breast in check for 32 years or longer, may occasionally be strong enough to cure it. I think the spontaneous cure of cancer may be more common than we have thought in the past.

DR. HARRY B. ZIMMERMAN, St. Paul: I should like to echo what Dr. Gatch has said. We know very little about cancer of the breast. The difference between one cancer of the breast and another cancer of the breast is just about as great as the difference between warts and carcinoma.

I don't have a 32-year result, but I did have a young woman upon whom my partner had operated and in whom he had found an inoperable cancer of the breast, inoperable by the ordinary technical procedures. He did an unfinished operation, and at the end of the operation it was a question of either ligating the major vessels and amputating the arm, or calling it a day.

I took care of that patient 10 years later because in that time my partner, who had operated on her, had died. She lived for 23 years and was doing her work for 23 years. There was never a time in those 23 years when, with a nickel's worth of procaine, I could not get a positive biopsy for cancer.

By the same token, I have had patients, as Dr. Gatch has mentioned, who died of disseminated cancer before they had a chance to leave the hospital. I had one patient that a doctor had sent to me to operate on for a procidentia. He said, "When you examine this patient, please don't look at her breast. She has a cancer of the breast. I would like to have her live until her child gets a little bigger. She wants to see her child married some day."

I did just that. I operated on her for procidentia and didn't touch the cancer of the breast. The youngster at that time was about 5 years old, and the patient lived to the day of the child's marriage. She never had anything done to her breast.

We just don't understand what is a metastasizing cancer and what isn't a metastasizing cancer. I have developed a sort of fatalistic feeling about cancer of the breast. I have seen incompetent surgeons do incompetent operations that were perfectly ridiculous, and they had excellent cures. I have seen the most competent radical operators operate and have the patients die in a very short time.

I don't know anything about cancer of the breast, and I have been operating on patients for it for a good many years.

DR. WILLIAM B. HUTCHINSON, Seattle: I should like to thank both Dr. Gatch and Dr. Zimmerman for their discussion. I think our main difficulty in cancer of the breast—the main problem—is the fact that we do not have a large enough series that has gone untreated, to know what the basic normal progress or normal history of the disease is. The only untreated series of any size is Daland's, which he reported some 20 years ago. In that series 22% of his patients with untreated carcinoma of the breast lived for 5 years, and 5% of them lived for 10 years.

DR. CHARLES S. SHERWIN, St. Louis: I should like to thank both Drs. Orr and Byars for their discussion.

Dr. Keyes asked me to emphasize that he employs a drain in the pectoralis area, that is, in the area of the pectoralis tendon, instead of a separate basting suture. On occasion I have used the basting suture in that area, as Dr. Orr has illustrated, and have had good results also by this method.

The variation in technique is apparent. Dr. Keyes has employed the suture without any material beneath it, and various materials, such as rubber dam drain or rubber tubing or gauze also have been employed, and each has shown good results.

SPONTANEOUS INTRACRANIAL HEMORRHAGE IN CHILDREN

Report of Eight Cases in Children Fifteen Years of Age or Younger

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ST. PAUL
AND
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SPONTANEOUS intracranial hemorrhage is a condition most frequently found in adults. It does occur in children, however, and, when present, the problems of diagnosis and treatment are, with a few exceptions, very similar to those in adults.

This report concerns spontaneous intracranial hemorrhage in eight children, 15 years of age or younger. All had proved hemorrhage by operation. Two deaths and six recoveries resulted. Four of these children were treated at the University of Minnesota Hospitals and four at other hospitals.

The commonest cause of spontaneous intracranial hemorrhage in children is a vascular anomaly, either aneurysmal or angiomatous. Hemorrhage from toxins, infectious diseases, blood dyscrasias, and tumors is rare.

It is the widespread opinion that aneurysms and other vascular anomalies of the brain are congenital in origin. Dandy [1] supported this view, and, more specifically, he thought that aneurysms could develop at sites where embryonic vessels or vascular buds had developed but had failed to disappear normally. Sugar [2] and Bassett [3] have expressed agreement with him. A different opinion has been expressed by Forbus,[4] who, enlarging on the work of Eppinger,[5] felt that aneurysms were acquired as the result of a congenital weakness of the media of an artery at its point of bifurcation and of a subsequent weakening of the intima followed by degeneration of the intima and aneurysmal dilatation of the artery. Dandy's explanation better accounts for the vascular anomalies, such as angiomas, than Forbus' theory, which is more applicable to aneurysms and their late rupture.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

1. Dandy, W. E.: Venous Abnormalities and Angiomas of the Brain, Arch. Surg. **17**:715-793 (Nov.) 1928; Arteriovenous Aneurysm of the Brain, ibid. **17**:190-243 (Aug.) 1928; Intracranial Arterial Aneurysms, Ithaca, N. Y., Comstock Publishing Co., Inc., 1944.

2. Sugar, O.: Symposium: Intracranial Vascular Abnormalities: Pathological Anatomy and Angiography of Intracranial Vascular Anomalies, J. Neurosurg. **8**:3-22 (Jan.) 1951.

3. Bassett, R. C.: Symposium: Intracranial Vascular Abnormalities: Surgical Experiences with Arteriovenous Anomalies of the Brain, J. Neurosurg. **8**:59-74 (Jan.) 1951

4. Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47**:239-284 (Nov.) 1930.

5. Eppinger, H.: Pathogenesis (Histogenesis und Aetiologie) der Aneurysmen einschliesslich des Aneurysma equi verminosum, Arch. klin. Chir. **35**:1-563, 1887.

There are other than congenital causes for some aneurysms. McDonald and Korb [6] in 1939 reported 30 cases of aneurysms in children out of 1,125 collected cases of saccular aneurysms in patients in all age groups, as verified by operation or autopsy. In 13 of these 30 cases, the aneurysms are recorded as being of embolic or thrombotic origin or associated with endocarditis.

Sands,[7] in 120 hospital patients with subarachnoid hemorrhage, found 16 with complicating infectious diseases. Of these 16 patients, 3 were children—1, aged 2 years, with measles; 1, aged 10 years, with congenital heart disease, and 1, aged 1 year, with whooping cough.

Baker and Shelden [8] report a high incidence of intracerebral hemorrhage associated with coarctation of the aorta due to the sustained incidence of cerebral hypertension in these cases. An aneurysm in a 13-year-old boy with coarctation of the aorta was reported by Strassmann.[9]

Infectious conditions as a cause of cerebral aneurysms or of hemorrhage undoubtedly play a small role in this chemotherapeutic bacteriostatic age.

The incidence of vascular anomalies in children is difficult to evaluate. In McDonald and Korb's series of 1,125 cases of aneurysm, 30 of the patients were children, as has been mentioned. Bassett in discussing 18 patients with arteriovenous anomalies of the brain includes 2 children under 15 years of age. Bagley [10] reports that of 24 patients with cerebral hemorrhage, 2 were children. Cushing and Bailey [11] report on 1 child with an aneurysm out of 14 patients with aneurysms. Jaeger [12] in reporting on 31 patients found no aneurysms of the intracranial carotid artery in children.

Dandy mentions 8 children in reporting on 32 patients with venous abnormalities, angiomas, and arteriovenous aneurysms. Of 108 patients with arterial aneurysms, there were 3 children 15 years of age or under. Only one of these children was considered to have a congenital aneurysm.

True aneurysms are the commonest vascular anomaly in adults, while angiomatous malformations are more usual in children. Richardson and Hyland,[13] who ex-

6. McDonald, C. A., and Korb, M.: Intracranial Aneurysms, Arch. Neurol. & Psychiat. **42**:298-328 (Aug.) 1939.

7. Sands, I. J.: Diagnosis and Management of Subarachnoid Hemorrhage, Arch. Neurol. & Psychiat. **46**: 973-1005 (Dec.) 1941.

8. Baker, T. W., and Shelden, W. D.: Coarctation of the Aorta with Intermittent Leakage of a Congenital Cerebral Aneurysm: Report of Case, Am. J. M. Sc. **191**:626-633 (May) 1936.

9. Strassmann, G., cited by McDonald and Korb.[6]

10. Bagley, C., Jr.: Blood in Cerebrospinal Fluid: Resultant Functional and Organic Alterations in Central Nervous System: Experimental Data, (July) 1928; Spontaneous Cerebral Hemorrhage: Discussion of 4 Types with Surgical Considerations, Arch. Neurol. & Psychiat. **27**:1133-1174 (May) 1932.

11. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C Thomas, Publisher, 1928.

12. Jaeger, R.: Aneurysm of Intracranial Carotid Artery: Syndrome of Frontal Headache with Oculomotor Nerve Paralysis, J. A. M. A. **142**:304-310 (Feb. 4) 1950.

13. Richardson, J. C., and Hyland, H. H.: Intracranial Aneurysms: Clinical and Pathological Study of Subarachnoid and Intracerebral Haemorrhage Caused by Berry Aneurysms, Medicine **20**:1-83 (Feb.) 1941.

tensively surveyed the literature on cerebral aneurysms, found that cerebral angiomas are rarely the cause of subarachnoid hemorrhage in adults but probably account for the majority of cases in childhood, when ruptured aneurysms, on the other hand, are very uncommon.

In addition to the 30 collected cases of aneurysm in children reported by McDonald and Korb, a search of the literature reveals 81 cases of spontaneous intracranial hemorrhage, or aneurysmal or angiomatous malformations in children. In 25 of these cases the cause of the hemorrhage was undetermined. Seventeen cases are designated as aneurysmal. In 39 cases some form of angioma is recorded. Thus approximately two-thirds of the proved vascular anomalies in children were angiomatous in character.

Determining the cause of spontaneous intracranial hemorrhage in children presents some difficulties not encountered in adults. Primarily, the problem is one of deciding whether or not the lesion is traumatic. With the well-known proclivity of children to bump their heads, a traumatic hematoma is frequently considered as a primary diagnosis. Members of the family can usually remember some head injury that the child has had in the near or distant past.

In the absence of a history of trauma, or acute toxic or infectious disease, or endocarditis or coarctation of the aorta, a diagnosis of either an aneurysm or other vascular anomaly can be made with reasonable certainty. The type and location can be determined only by angiography or ventriculography.

Numerous cases of spontaneous intracranial hemorrhage in children have been recorded in which recovery took place without any surgical intervention. Strauss and his associates [14] reported on a child, aged 10, convalescing after two attacks of subarachnoid bleeding. Kahan [15] reported that three children aged 12 years, 8¾ years, and 9 years, all recovered spontaneously, but all were more or less crippled. Miller [16] described three of five children with spontaneous subarachnoid hemorrhage who recovered without any special treatment. Ramsay's [17] patient, aged 10, recovered spontaneously. Sachs [18] in 1928 remarked that he was impressed by the fact that cerebral hemorrhage occurs in children and that the effusion is greater than in adults. Many survive, he states, but many are more or less crippled.

Despite the fact that there are patients who recover without surgery there can be little doubt that a surgical attack gives a better over-all result than the so-called conservative treatment.

Dandy's great stimulus to the surgical treatment of these conditions has led to successful treatment in many cases.

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14. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage: Its Relation to Aneurysms of Cerebral Blood Vessels, Arch. Neurol. & Psychiat. **27**:1080-1132 (May) 1932.

15. Kahan, A.: Spontaneous Subarachnoid Hemorrhage in Children, Brit. M. J. **1**:567 (March 17) 1951.

16. Miller, H. G.: Spontaneous Subarachnoid Haemorrhage in Children, Arch. Dis. Childhood **13**:258-263 (Sept.) 1938.

17. Ramsay, M. L.: Subarachnoid Haemorrhage in a Child, Brit. M. J. **1**:1070 (June 20) 1931.

18. Sachs, B.: Apoplexy, Bull. New York Acad. Med. **4**:1250-1257 (Dec.) 1928.

Mount's [19] report in 1951 on the treatment of spontaneous subarachnoid hemorrhage leaves little doubt of the efficacy of surgical treatment. Of 752 collected cases in which medical treatment was employed, 48% of the patients died. In 469 cases with surgical treatment the mortality was only 14%. Reports on surgically treated patients by Falconer,[20] Hamby,[21] Norlen,[22] Olivecrona,[23] Penfield,[24] Pilcher,[25] Poppen,[26] Schwartz,[27] and Swain [28] give further evidence that surgical intervention is indicated in the majority of instances.

REPORT OF CASES

The first two cases are somewhat similar in their rapid course and are the two fatalities of the eight cases.

CASE 1.—D. L., a 6-year-old boy, was admitted on June 22, 1952. He was deeply stuporous on admission. He had been hit on the eye two weeks previously with a soft sponge ball. For the 12 hours immediately after this accident, he had a headache and vomited but seemed to recover completely from this. On the day of admission he complained of a severe headache and rapidly became stuporous. He had many tonic and clonic seizures, and there was some suggestion of a left hemiplegia. His condition deteriorated so rapidly that immediate trephination was carried out in the hope that a subdural hematoma might be found. Both ventricles were found filled with blood. His condition was so severe that a ventriculostomy was done and nothing more. He died a few hours after surgery.

Postmortem examination revealed a large intracerebral clot in the right temporoparietal region, which had ruptured into the ventricles. When the clot was evacuated, a cavity 10 by 5 by 5 cm. remained. No abnormal vessels or other source of hemorrhage could be found, and it was assumed that a ruptured arterial aneurysm must have caused the hemorrhage even though it could not be identified.

Comment.—It is possible that if the intracerebral clot had been removed recovery might have taken place. The patient's condition did not warrant angiography.

19. Mount, L. A.: Treatment of Spontaneous Subarachnoid Hemorrhage, J. A. M. A. **146:** 693-697 (June 23) 1951.

20. Falconer, M. A.: Surgical Treatment of Spontaneous Subarachnoid Haemorrhage: Preliminary Report, Brit. M. J. **1:**809-813 (April 8) 1950.

21. Hamby, W. B.: Spontaneous Subarachnoid Hemorrhage of Aneurysmal Origin: Factors Influencing Prognosis, J. A. M. A. **136:**522-528 (Feb. 21) 1948.

22. Norlen, G.: Arteriovenous Aneurysms of the Brain: Report of 10 Cases of Total Removal of Lesion, J. Neurosurg. **6:**475-494 (Nov.) 1949.

23. Olivecrona, H., and Riives, J.: Arteriovenous Aneurysms of the Brain: Their Diagnosis and Treatment, Arch. Neurol & Psychiat. **59:**567-602 (May) 1948. Olivecrona, H.: Arteriovenous Aneurysms in Brain, Nord. med. **41:**843-886 (May 13) 1949, abstracted, J. A. M. A. **141:**878 (Nov. 19) 1949.

24. Penfield, W.: Operative Treatment of Spontaneous Intracerebral Haemorrhage, Canad. M. A. J. **28:**369-372 (April) 1933.

25. Pilcher, C.: Subcortical Hematoma: Surgical Treatment, with Report of 8 Cases, Arch. Neurol. & Psychiat. **46:**416-430 (Sept.) 1941. Pilcher, C.; Meachem, W. F., and Cobb, C. A.: Surgical Treatment of Intracranial Angiomatous Malformations, Surgery **28:**342-349 (Aug.) 1950.

26. Poppen, J. L.: Symposium: Intracranial Vascular Abnormalities: Specific Treatment of Intracranial Aneurysms: Experiences with 143 Surgically Treated Patients, J. Neurosurg. **8:** 75-102 (Jan.) 1951.

27. Schwartz, H. G.: Subarachnoid Hemorrhage and Intracranial Aneurysm, Postgrad. Med. **4:**307-314 (Oct.) 1948.

28. Swain, R. D.: Surgical Treatment of Certain Intracranial Arterial Aneurysms, S. Clin. North America **28:**396-404 (April) 1948.

Although an aneurysm could not be verified, it is our opinion that such was the cause of the hemorrhage. In the words of William Gull, "Recent coagula may so imbed and conceal it that unless strictly looked for, it will not be found for the sac is often small and thin and transparent." [29]

CASE 2.—R. S., a 9-year-old boy, was admitted to the hospital on April 15, 1952. On the day of admission, while at school, he experienced a sudden severe headache, which was followed by a generalized seizure and coma. When first examined about six hours later he was deeply stuporous, with evidence of a right hemiplegia. The spinal fluid was grossly bloody, and the pressure was 600 mm. of water. His condition was considered so critical that an immediate

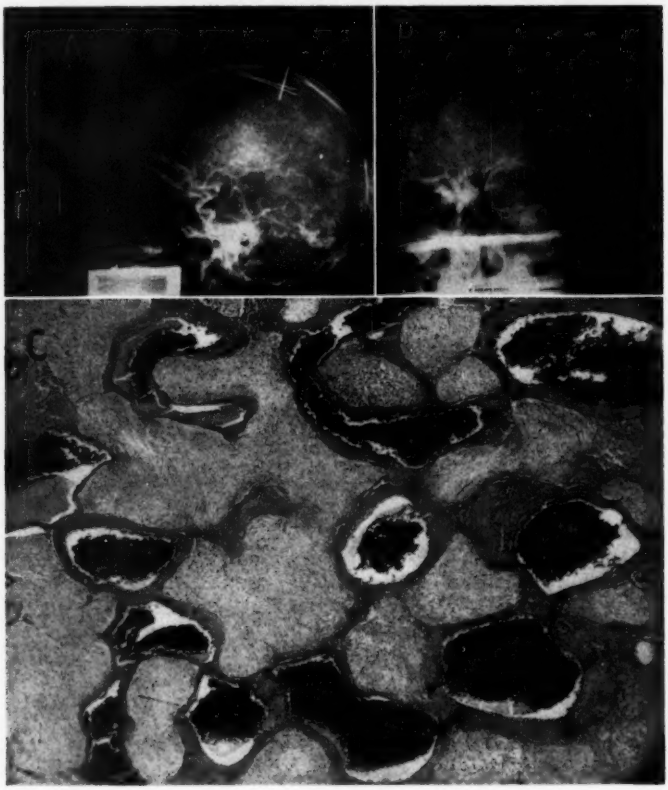

Fig. 1 (Case 3).—*A*, lateral carotid angiogram. *B*, posteroanterior carotid angiogram. *C*, photomicrograph of angioma.

exploration was deemed advisable without further diagnostic procedures. A large intracerebral hematoma was located in the left parietal region and was removed, leaving a cavity 10 by 5 by 3 cm. Many abnormal vessels were observed in the area.

The patient failed to improve and died a few hours after surgery.

Postmortem examination revealed no further clot, but a mass of vessels was present in the operative area. Microscopic sections demonstrated an angiomatous structure.

29. Gull, W.: Aneurism of Cerebral Vessels: 6 Cases, Guy's Hosp. Rep. **5**:281-304 (Series 3) 1859.

Comment.—An angiomatous malformation was the cause of hemorrhage in this case. Neurosurgical consultation was delayed six hours, and at that time his condition was too critical for angiography.

In the next three cases the malformations were angiomatous, as proved by angiography. The patients were not in critical condition when seen, and surgical intervention resulted in recoveries in all three.

CASE 3.—R. G., aged 8 years, was admitted with a three-day history of vomiting, general malaise, headache, and one generalized seizure. The spinal fluid revealed gross blood. Expectant treatment was carried out until the 15th day when a carotid angiogram was made which revealed a mass of abnormal vessels at the occipital pole on the right side. A left homonymous hemianopsia was also noted. On the 17th day a craniotomy revealed a cystic cavity in the right occipital lobe, containing old clotted blood. The clot and a small mass of vessels were removed. Microscopic examination revealed an arterial type of angioma (Fig. 1).

Fig. 2 (Case 4).—*A* and *B*, carotid angiograms. *C*, postoperative x-ray showing clips in operative area.

Sixteen months following operation the patient was asymptomatic except for a persistent left homonymous hemianopsia.

CASE 4.—D. K., an 11-year-old boy, was admitted on March 25, 1952, with a three-day history of headache, vomiting, and drowsiness. No history of injury could be elicited, although his activities on the day of onset could not be determined since he was away from home all day. On first examination he had a right hyperflexia, a slight aphasia, early papilledema, and blood-tinged spinal fluid with a pressure of 500 mm. of water. He became progressivly more stuporous, and five hours after admission bilateral trephination revealed a hematoma in the right frontal region. An angiogram was immediately performed and revealed an arteriovenous malformation in the right frontal area. A transfrontal craniotomy was done and a large intracerebral hematoma evacuated, and several large vessels were clipped.

Eight months later he was without complaint and was neurologically normal (Fig. 2).

CASE 5.—W. R., a 10-year-old boy, was admitted to the hospital on June 15, 1952, with a history of sudden onset, 12 hours previously, of headache, vomiting, slurred speech, and left hemiparesis. The spinal fluid revealed 4,220 red blood cells per cubic centimeter. Within 10 days he was considerably improved, and a right carotid angiogram revealed an arteriovenous malformation in the right parietal region. A block excision of this area was carried out and a large intracerebral hematoma evacuated.

The child was slowly improving six weeks after operation but still had a left-sided weakness (Fig. 3).

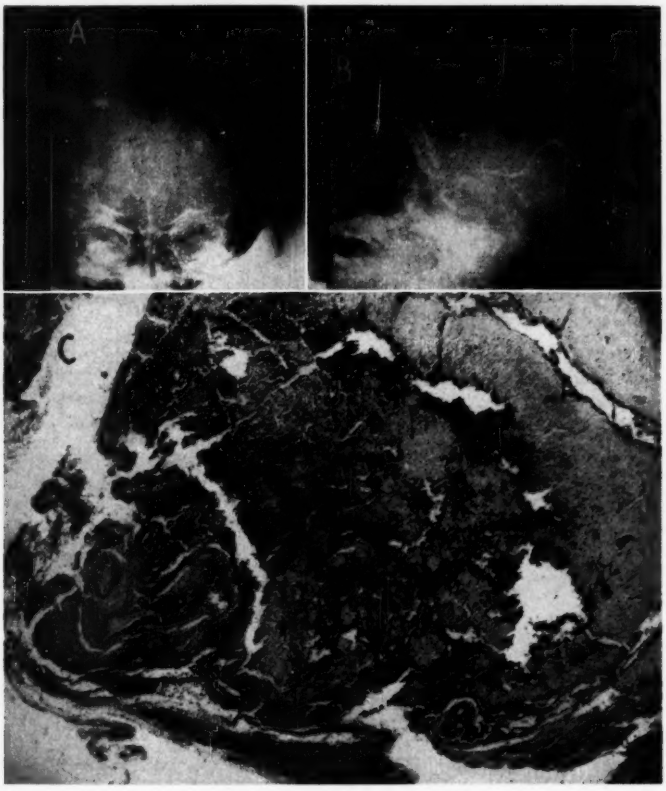

Fig. 3 (Case 5).—*A*, posteroanterior carotid angiogram. *B*, lateral carotid angiogram. *C*, photomicrograph showing interstitial hemorrhage with numerous vessels.

Comment.—These three cases illustrate the manner in which angiography is of great aid in successful treatment. The onset and progression of illness, except in Case 4, was slow enough to warrant a more satisfactory study. In Case 4 angiography might better have been done before trephination. Nevertheless, angiography, even after the hematoma had been located, still gave valuable aid in the localization of the feeding vessels so that they could be readily exposed and clipped.

In the remaining three cases the etiologic factors are unproved. In one instance angiography was unsuccessful. In another instance angiography was not done because the Matas test was definitely positive. In the third instance angiography

was not done because a vascular lesion was not considered in the differential diagnosis. However, ventriculography revealed deformities leading to operation in all three cases.

CASE 6.—F. S., a 13-year-old boy, was admitted to the hospital on Oct. 28, 1951. One week before admission he complained of a moderately severe nonlocalized headache. Two days before admission he complained of poor vision in the left eye, and vision had deteriorated to light perception by the time he was admitted. His headache persisted and grew progressively severer. Spinal puncture demonstrated a clear fluid under normal pressure. Visual field determination revealed a normal field in the right eye. A ventriculogram revealed flattening of the extreme anterior portion of the third ventricle. A preoperative diagnosis of a possible craniopharyngioma was made, and the suprasellar area was explored.

The left optic nerve was compressed from below by a mass. The mass was aspirated, and no fluid or blood was obtained. The capsule was opened and a few pieces of dark granular

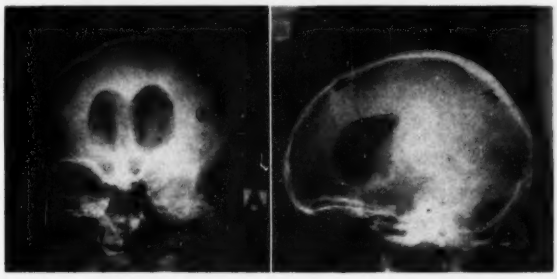

Fig. 4 (Case 7).—Posteroanterior and lateral ventriculograms showing a mass projecting into left lateral ventricle.

Fig. 5 (Case 8).—Posteroanterior and lateral ventriculograms showing cystic cavity in left frontal area.

material removed. At this point tremendous bleeding occurred, and it was felt that a large aneurysm of the internal carotid artery had been entered. The hemorrhage was eventually controlled by ligating the carotid artery in the neck and packing the bleeding area with gelfoam.[3]

His postoperative course was surprisingly uneventful. His vision rapidly returned, and at present, one year after surgery, the boy is symptom-free; his vision is the same as it was prior to his illness, and he now carries on all his previous activities, except that he has given up playing the tuba in his high school band.

An aneurysm was not verified with absolute certainty, but the operative findings and subsequent course make it almost certain that this boy had an aneurysm of the intracranial portion of the carotid artery.

CASE 7.—J. M., a 12-year-old boy was admitted to the hospital on Jan. 4, 1950, with a history of awakening 13 days previously with a headache, stiff neck, and vomiting. The spinal fluid withdrawn shortly after onset of the illness was grossly bloody. He improved for a few days

after onset but had a recurring episode of headache, and again there was fresh blood in the cerebrospinal fluid. On admission to the hospital he was semiconscious and had papilledema and a left hemiparesis. A right carotid angiogram revealed no abnormalities. A left carotid angiogram was unsuccessful. A ventriculogram revealed a deformity of the left lateral ventricle consistent with a mass (Fig. 4).

A craniotomy revealed a blood clot occupying the entire left ventricle. The clot was totally removed and several small bleeding points clipped. About 30 days after operation angiograms were repeated but failed to show any abnormalities. On last examination, 31 months following discharge, he was symptom-free, doing fairly well in school, and was neurologically normal except for a slight inequality in deep reflexes.

CASE 8.—A. B., aged 12 years, was admitted to the hospital on Dec. 1, 1948, with a history that four days prior he had suffered a minor fall and 24 hours later there was the onset of headache, vomiting, and lethargy. On admission he was alert but complained of headache and stiff neck. The spinal fluid was grossly bloody, and the pressure was 105 mm. of water. A diagnosis of subarachnoid hemorrhage was made, and he was maintained on bed rest. Nineteen days after admission there was evidence of fresh bleeding with a right hemiparesis. An angiogram was contemplated, but the Matas test was definitely positive; consequently it was not done, and the patient was treated expectantly. About two weeks later a ventriculogram revealed a symmetrical hydrocephalus and a cyst which became filled with the injected air in the left frontal lobe (Fig. 5).

A left transfrontal craniotomy revealed a large intracerebral hematoma, containing 4 oz. of old blood, which was removed. He recovered rapidly.

Three and one-half years after operation he was well except for a slight residual limp.

No definite etiological factor was identified in this instance.

Comment.—Although angiography is the ideal method of demonstrating these lesions, on occasions it is not done or is unsuccessful. In these instances ventriculography is of great aid in localizing these hemorrhages.

CONCLUSIONS

It is interesting to note that in the four cases in which the cause was definitely proved, angiomatous malformations were present. The diagnosis in one other case was in our opinion, an aneurysm of the intracranial portion of the internal carotid artery. In the remaining three cases, no cause was proved. The two deaths were from massive and rapid hemorrhage.

Spontaneous subarachnoid hemorrhage in children, as a rule, arises from a congenital vascular anomaly, usually angiomatous in nature. Successful treatment depends upon accurate localization and surgical intervention. Angiography has been of great value in the diagnosis of these lesions.

"PLICATION"

Method of Reducing the Caliber of Vein Grafts

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VENOUS grafts in the arterial tree have been used extensively in experimental surgery and in a number of instances in clinical work.[1] Veins have the advantage of being readily available and of being autogenous vascular tissue which may be obtained without the sacrifice of vital parts or functions, as is the case with arteries. A vein of proper diameter cannot always be secured, however. The disadvantages of grossly oversized veins are the high incidence of early thrombosis, rupture at the suture lines, and excessive later dilatation. The latter factor is probably related more directly to the musculofascial support of an autogenous vein graft rather than to the graft-aortic disproportion present at the time of implantation.

Carrel [2] described a method of reducing the caliber of vessels *in situ* by means of horizontal mattress sutures, which he termed "longitudinal exclusion," but did not, to our knowledge, employ it on free graft segments.

In the course of our experiments with venous grafts in the laboratory we became aware of the need for a method that would enable the operator to reduce the diameter of an oversized vein graft by any desired degree.

From the Department of Surgery, University of Washington School of Medicine.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

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1. (*a*) Blakemore, A. H.: Restorative Endoaneurysmorrhaphy by Vein Graft Inlay, Ann. Surg. **126**:841-849 (Dec.) 1947. (*b*) Cooke, F. N.; Hughes, C. W.; Jahnke, E. J., and Seeley, S. F.: Homologous Arterial Grafts and Autogenous Vein Grafts Used to Bridge Large Arterial Defects in Man: A Report of 14 Cases, Surgery **33**:183-189 (Feb.) 1953. (*c*) Johnson, J.: Kirby, C. K.; Greifenstein, F. E., and Castillo, A.: The Experimental and Clinical Use of Vein Grafts to Replace Defects of Large Arteries, Surgery **26**:945-956 (Dec.) 1949. (*d*) Smith, M. K.: Arterial Injuries, Ann. Surg. **126**:866-872 (Dec.) 1947. (*e*) Swan, H., and Morfit, H. M.: Arterial Homografts: Use of Preserved Grafts in the Treatment of Neoplastic Disease Involving Peripheral Arteries, A. M. A. Arch. Surg. **62**:767-775 (June) 1951.

2. Carrel, A.: The Surgery of Blood Vessels, Bull. Johns Hopkins Hosp. **18**:18-28 (Jan.) 1907.

METHOD

The method evolved by us is briefly as follows: After the graft was anastomosed and distended with blood under arterial pressure, the diameters and circumferences of the graft and recipient vessel were determined by caliper and string measurements. The amount of diameter reduction necessary was calculated and the appropriate width of vein wall measured with calipers. The vein graft was then plicated by means of interrupted Lembert-type sutures placed about 2 mm. apart. By using oiled 6-0 nonabsorbable surgical (silk) suture material on a sharp Atraumatic needle, it was possible to place most of the sutures without penetrating the intima. The sutures were so placed that the entire width of vein wall, which was infolded, was encompassed by each stitch (Fig. 1). Some bleeding occurred if penetrating needle holes were present, but such bleeding was easily controlled by light digital pressure. A continuous Lembert-type suture was used in some experiments, but we found that it was less satisfactory than the interrupted type because of greater difficulty in controlling bleeding from needle holes and the lessened flexibility of diameter control. If bleeding was troublesome because of numerous punctures through the entire wall, application of the Pott's clamp proximal to the upper anastomosis for a few moments reduced the pressure within the graft sufficiently to allow sealing of the holes, with resultant minimal blood loss. On completion of the plication, measurements were again taken and further plication stitches placed, if necessary, to obtain satisfactory diameter reduction of the vein graft.

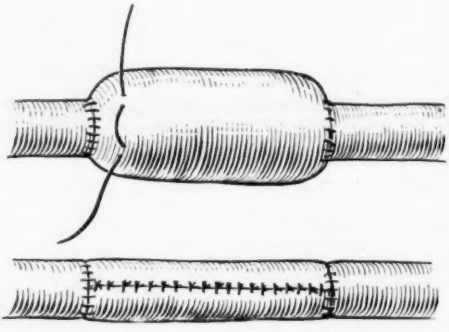

Fig. 1.—Diagram of method of plicating venous autografts. Above, first plicating suture; below, plication completed.

RESULTS

We have used this method to reduce the diameter of fresh inferior vena caval autografts implanted into the abdominal aortas of 10 adult dogs and 12 weanling pigs with satisfactory results. Similar groups of animals with unplicated grafts were used as controls. All operations were done under strict aseptic precautions.

The incidence of thrombosis in the pigs with plicated grafts did not differ significantly from that in the control series with unplicated grafts. The grafts in the pigs were of short length (range, 2.2 to 4.2 cm.) with one exception, a graft of 5.2 cm. long. We have previously reported [3] that the incidence of early thrombosis in oversized venous grafts is much lower in grafts under 5.0 cm. in length than in those over 5.0 cm. in length. Examination of the plicated vein segments at the time

3. Schmitz, E. J.; Kanar, E. A.; Sauvage, L. R.; Storer, E. H., and Harkins, H. N.: The Influence of Diameter Disproportion and of Length on the Incidence of Complications in Autogenous Venous Grafts Implanted in the Abdominal Aorta, Surgery **33**:190-206 (Feb.) 1953.

of slaughter, when the pigs had matured and increased in weight from 600 to 1,000%, indicated that the vessels increased in length and diameter, as did the unplicated specimens (Fig. 2).

A striking difference in the incidence of early thrombosis occurred in dogs with grafts over 5.0 cm. in length. Eight dogs had unplicated grafts more than 20% larger in diameter than the recipient abdominal aorta. This group of dogs with

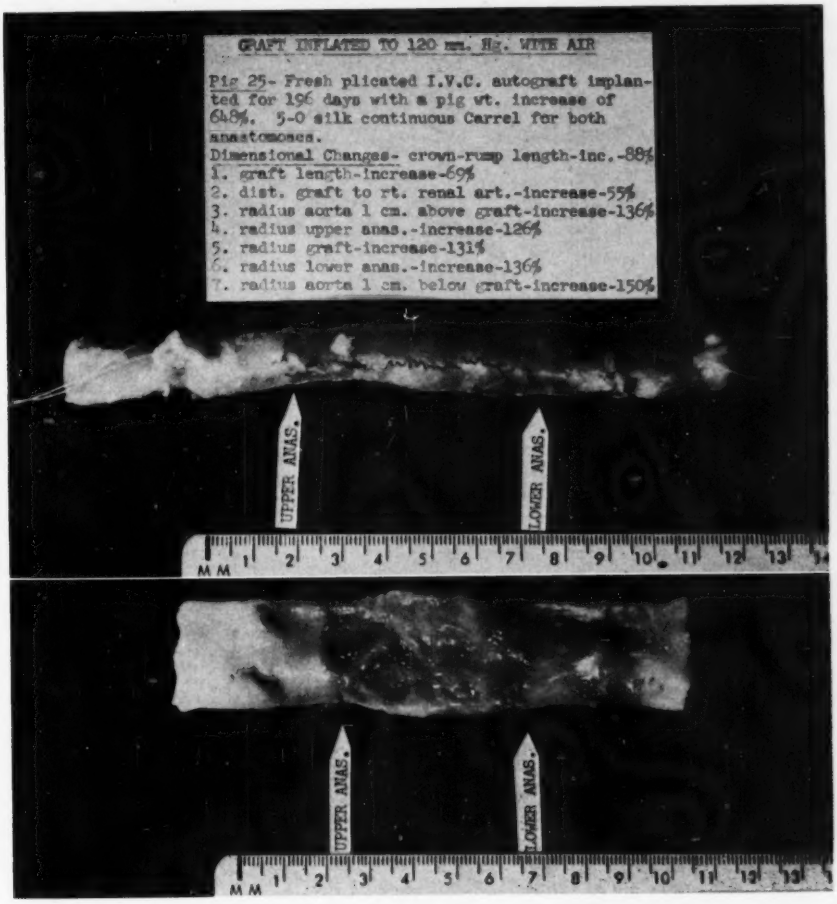
GRAFT INFLATED TO 120 mm. Hg. WITH AIR
Pig 25- Fresh plicated I.V.C. autograft implanted for 196 days with a pig wt. increase of 648%. 5-0 silk continuous Carrel for both anastomoses.
Dimensional Changes- crown-rump length-inc.-88%
1. graft length-increase-69%
2. dist. graft to rt. renal art.-increase-55%
3. radius aorta 1 cm. above graft-increase-136%
4. radius upper anas.-increase-126%
5. radius graft-increase-131%
6. radius lower anas.-increase-136%
7. radius aorta 1 cm. below graft-increase-150%
UPPER ANAS.
LOWER ANAS.
MM
UPPER ANAS.
LOWER ANAS.
MM

Fig. 2.—Upper, photograph of plicated inferior vena caval autograft to abdominal aorta of small pig, removed after the animal had reached maturity. Graft inflated to pressure of 120 mm. Hg with air. Note superficial position of plication suture at this time. Continuous plication suture has not interfered with growth of graft. Lower, open view of above specimen. Line of plication is not discernible on intimal surface.

unaltered grafts served as controls. Seven (87%) of these control unplicated dogs either died of early thrombosis in the graft (six dogs) or of suture line separation (one dog) within the first two weeks. One graft (13%) has remained open and

functioning 14 months after graft implantation, or up to the time of this report. These data are presented in Table 1. Because the control series, with the exception of one dog, did not contain long-term survivors, this study does not permit us to compare the incidence of late complications in the plicated group with that in the controls.

TABLE 1.—*Measurements and Early Complications Occurring with Control Group of Oversized Inferior Vena Caval Autografts to the Abdominal Aorta*

Dog No.	Graft Length, Cm.	Graft Diameter, Cm.	Aortic Diameter, Cm.	% Oversize	Early Complication
R-100	7.4	1.0	0.6	66	Thrombosed at 1 day
C-7	10.5	1.3	0.65	100	Thrombosed at 11 days
R-41	9.0	1.6	0.85	88	Thrombosed at 4 days
C-62	8.9	1.5	0.85	76	Thrombosed at 1 day
C-77	7.3	1.2	0.85	41	Living after 14 mo.
C-80	6.5	1.4	0.80	75	Rupture of suture line at 8 days
C-83	9.5	1.3	0.90	44	Thrombosed at 1 day
C-79	7.7	1.0	0.60	66	Thrombosed at 1 day

Incidence of early complications 87%

TABLE 2.—*Measurements and Complications Occurring with Plicated Inferior Vena Caval Autografts to the Abdominal Aorta*

Dog No.	Graft Length, Cm.	Graft Diameter, Cm.	Aortic Diameter, Cm.	% Oversize	Graft Diameter After Plication, Cm.	% Oversize After Plication	Early Complications	Late Thrombosis	Present Status
C-53	7	1.35	0.8	68	0.95 *	18	None	None	Dead
C-61	9.8	1.35	0.75	80	0.75 *	0	None	Thrombosed at 2½ mo.	Dead
C-68	5.9	1.2	0.8	62	0.8 *	0	None	None	Dead
E-16	7.3	1.2	0.75	60	0.9	20	None	None	Alive
A-44	7.5	0.8	0.55	31	0.52 *	5% smaller	None	None	Dead
E-7	6.3	0.8	0.60	33	0.7	16	None	None	Dead
E-85	5.6	1.05	0.65	61	0.65	0	None	None	Alive
E-86	7.5	1.15	0.7	64	0.75	7	None	None	Alive

Incidence of early complications 0%

* These dogs had continuous plication; other dogs, interrupted sutures.

Ten dogs had similar venous autografts implanted into the abdominal aorta, and the diameter of the grafts was immediately reduced by means of plication. There were no early thromboses noted in this group. The data on this group of dogs are detailed in Table 2. (Two dogs with plicated grafts with continuous plication suture died during the first two weeks postoperatively. Autopsy revealed no evidence of thrombosis. These dogs are not included in Table 2.) Aortography revealed that one dog (C-61), or 13%, had a closure of the graft 10 weeks postoperatively. This graft was found open by aortography five and one-half weeks

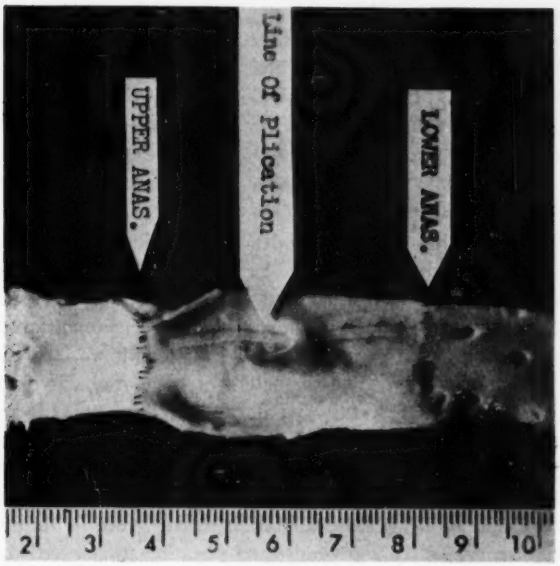

Fig. 3.—Photograph of opened fresh inferior vena caval autograft removed from dog (C-68) 41 days after implantation into abdominal aorta with continuous plication of graft.

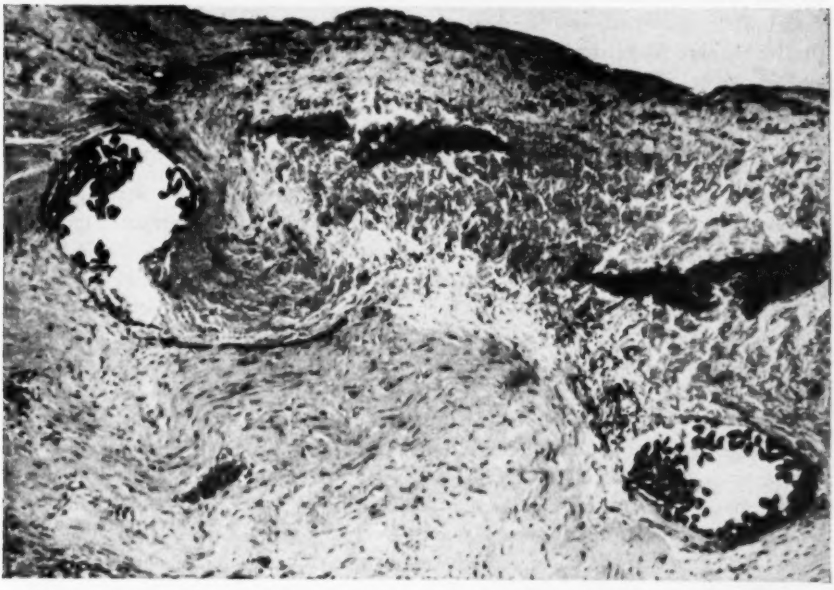

Fig. 4.—Photomicrograph (× 20) of cross section through line of plication of specimen shown in Figure 4. Intimal surface is at top of Figure. Note in upper left-hand corner of Figure how endothelium has grown in and filled depression caused by plication. Remnants of the continuous silk suture are seen in cross section.

postoperatively, but there was evidence suggesting that nonocclusive thrombosis was present at that time. Of the remaining eight animals, three (E-16, E-85, and E-86, Table 2) are alive (eight, five, and five months, respectively, after implantation of the plicated grafts); three (C-53, C-68, and A-44) have died of mesenteric thrombosis within 48 hours of aortography (two dogs, one and one-half months, and one dog, six months after graft implantation), and one dog (E-7) died of inanition (possibly due to an associated gastric operation) four and one-half months after implantation of the graft.

The dogs that are living show no evidence of weakness of the hind limbs or other signs of thrombosis of the grafts. The dogs that died of mesenteric thrombosis associated with aortography showed no x-ray or necropsy evidence of thrombosis or lack of patency of the grafts. The dog that died of inanition demonstrated the following interesting growth changes. The graft length was 6.3 cm. at implantation and 5.7 cm. at necropsy. The diameters of the aorta above and below the graft were 0.6 and 0.6 cm., respectively, at implantation and 1.0 and 0.97 cm., respectively, at necropsy. The graft diameters in the upper, middle, and lower thirds of the graft were respectively as follows: at implantation before plication, 0.8, 0.7, and 0.9 cm.; after plication, 0.6, 0.6, and 0.7 cm., and at necropsy, 1.0, 1.0, and 1.2 cm., demonstrating some dilatation of the graft. Additional observations on the late dimensional changes following plication in comparison with unplicated grafts will be the subject of a separate report.

Examination of the plicated segments of vein grafts from seven days to six months after operation revealed that the sutures were covered by endothelium, the vessel walls thickened, and the line of plication barely discernible. In some cases the suture line was palpable as a cord-like area in the wall of the vessel (Figs. 2 and 3). The microscopic appearance of a typical plicated segment approximately 60 days postoperatively is shown in Figure 4.

COMMENT

Swan [4] has repeatedly emphasized the necessity of accurate matching of the vessel caliber if optimum results are to be obtained in graft operations. Since such matching is frequently not possible without altering the caliber of available venous grafts, it then becomes necessary to do so by artificial means. The factors responsible for failure of venous autografts are early thrombosis, suture line dehiscence, rupture of the graft, late thrombosis, and excessive dilatation. In a previous report [5] we have shown that in grossly oversized venous autografts over 5 cm. in length, thrombosis is the most frequent cause of early failure. Turbulent blood flow, as well as reduced velocity of flow, in oversized grafts over 5 cm. long permits the sedimentation of formed blood elements on the damaged intima and suture material at the lines of anastomosis leading to the formation of an occlusive thrombus. Smith [5] has demonstrated that in the isodimensional vessel the blood stream consists of an axial core of formed elements surrounded by a peripheral clear zone. When turbulence in the blood flow disrupts this arrangement, the formed elements

4. Swan, H.; Robertson, H. T., and Johnson, M. E.: Arterial Homografts: The Fate of Preserved Aortic Grafts in the Dogs, Surg., Gynec. & Obst. **90**:568-579 (May) 1950.

5. Smith, S.: Studies in Experimental Vascular Surgery, Surgery **18**:627-643 (Nov.) 1945.

come in contact with the intimal surfaces and settle out on any damaged areas. This may explain why we have noted such a low incidence of thrombosis in our plicated vessel segments even in the presence of larger amounts of exposed foreign material (sutures) and the intimal damage associated therewith, since the plicated graft and recipient vessel are very nearly isodimensional.

The plication procedure is of value because of the improvement in hemodynamics that results from its use and the consequent lowered incidence of early thrombosis. Plication did not seem to have any effect on the subsequent dimensional changes in the graft. It should not be considered a substitute for a graft of proper caliber when such is available.

SUMMARY

Longitudinal plication is presented as a method of reducing the caliber of vein grafts to fit the recipient vessel.

This technique has proved satisfactory, in our hands, in decreasing the incidence of thrombosis in such grafts during the early postoperative period.

The incidence of late thrombosis was also low (13%) in the plicated group, but comparison with the control series is difficult because there was only one late survival among the control animals.

SURGICAL DIVISION OF THE PATENT DUCTUS ARTERIOSUS

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CHICAGO

SURGICAL closure is now the uniformly accepted method of treatment of the patent ductus arteriosus. Whether a ductus is ligated or divided is largely a matter of individual preference. In our early work my colleagues and I ligated 21 consecutive ducti. Although examinations during the immediate postoperative period revealed no evidence of incomplete closure and later follow-up examinations brought to light no suspicion of recanalization, we prefer division and suture and for the following reasons: It is very difficult to know exactly how much tension to put on ligatures when tying a ductus—too little, and the ductus is incompletely occluded—too much, and the ligature cuts through. It is not desirable to bury large amounts of nonabsorbable heavy suture material about the bronchus and large vessels. Late recanalization cannot occur if the ductus has been cut and sutured. With proper technique there is less danger of operative hemorrhage when dividing than when ligating a ductus.

This paper is based on a study of 214 operations for patent ductus arteriosus in children, ranging in age from 10 months to 15 years, who have been operated upon at Children's Memorial Hospital by the attending and resident surgical staff. The first 21 ducti were ligated, and the next 193, without exception, were divided and sutured.

It is worthy of special note that the diagnosis, made by Dr. Stanley Gibson and associates, was proved correct at operation in all but one case. That one patient, the 201st, had the characteristic continuous raucous murmur and all the other classic findings but at operation had no ductus arteriosus. Success was long lived but eventually fell, failure occurred as it always must.

PREOPERATIVE CARE

It is routine to have the child admitted to the hospital approximately 48 hours before operation. This time not only allows for further study and repeated auscultation of the murmur by those of the staff who are interested but also furnishes ample opportunity for observation of the beginning of an upper respiratory infection. If the slightest sign of a cold presents itself, the child is sent home and given a later appointment. Occasionally, a typical upper respiratory infection does not develop after the patient returns home. Parental irritation is promptly assuaged when it is explained how foolhardy it is to give a child with even the slightest cold an intratracheal anesthesia for an operation which is elective.

From the Department of Surgery, Children's Memorial Hospital.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

The child is prepared psychologically for the operation first of all by treating him as an intelligent human being who likes to know what is going to happen and is entitled to an explanation in understandable terms. Fooling a child who has reached the age of reason is a mistake. The younger child is simply told that the following morning he will have a ride on a cart while mother stays in the room and that when he gets upstairs he will have fun blowing up a colored balloon. The older child is told in understandable terms that he is to have an operation and why, that he will be given some not unpleasant gas, will go to sleep, feel no pain, and later will wake up in his room where mother and daddy will be waiting for him. (These fine explanations are not always accepted.) If the mother remains in the room with the child the night before operation she is given the pentobarbital (Nembutal).

Preoperative medication consists only of administration of morphine and scopolamine in such liberal doses that the patient is "mellow," not sleepy, and mildly interested in his surroundings when arriving in the operating room. An average 5- to 12-year-old child will require morphine sulfate, ⅛ grain (8.0 mg.), balanced with scopolamine hydrobromide, 1/200 grain (0.30 mg.), given hypodermically one hour before operation.

ANESTHESIA

What the surgeon wants in the way of anesthesia for operative closure of a patent ductus is smooth induction, constant complete oxygenation, a strong regular pulse, a quiet operative field, quick recovery, and few postoperative respiratory complications. As a matter of fact, progress in the field of anesthesia has been such that these objectives are usually attainable. These objectives have been fulfilled in a large measure by Drs. W. O. McQuiston and John Burdon, who have given practically all the anesthesias for these operations.

Simplicity is the keynote of success in any venture, and nowhere is it more applicable than in anesthesiology. Multiple anesthetic agents given at the same time or in quick sequence may make the anesthesia appear smooth, but actually, they do so by covering up some of the signs that indicate danger. Parenthetically, I should like to say that for infants and children I think the intravenous injection of thiopental (Pentothal) sodium is dangerous, that curare is arrow poison and should remain so, that procaine hydrochloride used intravenously is highly overrated, and that spinal anesthesia has no place in a children's hospital.

The child is quickly rendered unconscious by a few whiffs of cyclopropane. Ether is added to produce sufficient relaxation to allow easy introduction of the intratracheal tube. After intubation the child is carried through the operation in a light plane of anesthesia on cyclopropane and oxygen alone. The to-and-fro technique with controlled respiration is used routinely. The advantages of this technique are tremendous. Far better oxygenation of the patient is maintained this way than by allowing the patient to breathe spontaneously or by assisting respiration. With the patient under controlled respiration, the mediastinal structures are motionless —a great aid to smooth surgical technique.

Some rise in temperature occurs in the patient during practically every operation of any magnitude, especially during the hot summer months. In order to keep the temperature near normal during ductus operations, we routinely place a

large rubber mattress with an intake and outflow tube, actually a large hot water bottle, under the patient on the operating table. Through this mattress cool or cold water is run as needed during the operation. By means of a thermocouple inserted in the patient's rectum and an electrically operated temperature recording device, the anesthesiologist may know at all times what the temperature is and can govern use of the cooling mechanism to control it.

Probably it is not important to keep the temperature near normal in patients whose oxygen uptake by the blood is normal, but certainly an elevation to 103 F. or above, a not uncommon occurrence without temperature control, is capable of doing the patient harm. On the basis of a 7% increase in metabolism with each degree of elevation in temperature, oxygen consumption is 30% greater when the patient's temperature is 103 F. than it is when the temperature is 99.0 F. Needless to say, the oxygen intake must be increased to meet the extra demands made by the hyperthermic patient. If added oxygen is not given to the unconscious overheated patient, hypoxia with all its attending calamities must result. The fact that the anesthesiologists and the entire surgical staff are constantly anxiously alert to the importance of adequate oxygenation during every moment of anesthesia may be, in part, the reason that we have not been harassed by cardiac irregularities of any consequence during patent ductus operations.

OPERATION

The patient is placed supine upon the operating table. As soon as anesthesia is sufficient a polyethylene tube is inserted into the saphenous vein of the right ankle. Without exception, a minimum of 500 cc. of blood is actually available in the operating room and more is stored in the bank. The patient is turned on the right side with the left arm drawn upward to elevate the scapula. A fairly long skin incision is made beginning about 3 cm. lateral to and below the left nipple and extending posteriorly below the scapula and curving upward to approximately the base of the fourth rib (Fig. 1*A*). In our early work a left submammary incision was loyally used as advised in the East. A disbelieving visitor from the far West proposed a posterolateral incision, which was apologetically tried but enthusiastically adopted. It allows a more adequate exposure of the aorta—an extremely valuable aid in averting difficulty or in getting out of trouble when dealing with large and/or short ducti. Adequate exposure of the ductal region is obtained by entering the chest through the fourth interspace. We never resect a rib for a ductus operation in patients up to 16 years of age. As the ribs are widely spread, the operator looks down on infallible guides to the position of the ductus: The phrenic nerve, the arch of the aorta, and the left pulmonary artery can all be seen and identified at a glance (Fig. 1*B*). Lateral to the phrenic nerve, immediately superior to the left pulmonary artery, and medial to the aorta lies the ductus. Its position is unmistakably confirmed by the palpating finger which feels the characteristic thrill.

A longitudinal incision is made in the parietal pleura over the left pulmonary artery upward just lateral to and parallel with the phrenic nerve. Beneath the pleura in the region directly inferior to the ductus lie a number of lymph glands. If in the way, they are removed. As this is being done and as the flaps of pleura

are being raised, the vagus nerve comes into view. Arising from it is the recurrent laryngeal nerve, which never fails to wind around the ductus and lead the surgeon unerringly to its inferior border (Fig. 2*C*).

Now comes the most important step in the operation—freeing the ductus from the surrounding tissues. Assuming that the operator is right-handed, the left hand performs the most consequential function. With the left hand the operator holds and guides the blunt tissue forceps that grasp the loose tissue which is to be cut by the scissors held in the right hand. The scissors used in all cardiovascular work is the long-handled Mentzenbaum type with slightly curved blades (Fig. 3). The blades are ground down, as suggested by Dr. Sidney Smith, so that the surgeon has thin flat opposing surfaces at the tip and can see exactly where and what they are cutting (Fig. 2*D*).

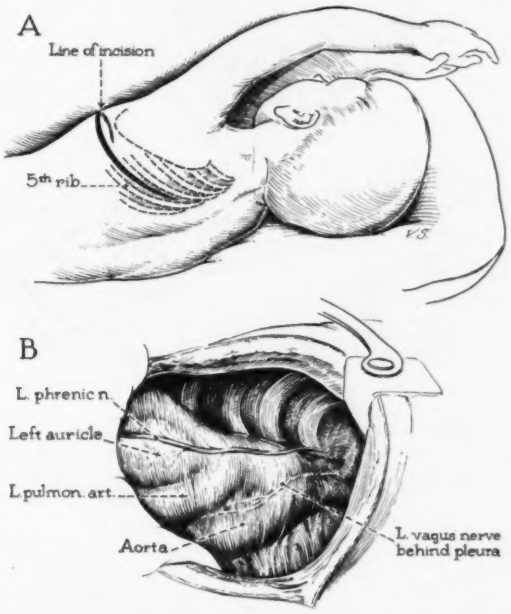

Fig. 1.—*A*, incision is made through left fourth interspace. *B*, phrenic nerve, pulmonary artery, and arch of the aorta are plainly visible when chest is opened, and within the triangle made by these structures lies the ductus.

The vagus nerve is thoroughly freed from surrounding tissue and gently retracted laterally by the assistant. The loose fibrous tissue over the anterior surface of the aortic end of the ductus is picked up and cut. Often the tip of the pericardial lappet extends well onto the aorta and will be included in the mass of fibrous tissue. One should always maintain a healthy fear of damaging the aorta, but actually one can easily and unmistakably recognize the grey-white wall of the aorta as the pericardial lappet and attached fibrous tissue are raised. The web-like adventitial layer between the pericardial lappet and the aorta is the definite line of cleavage which must be and can be followed easily. Through this layer the peri-

cardial lappet is carefully and painstakingly dissected from the ductus. Progress is made easily and safely if the left hand fulfills its function of grasping the tissue to be removed and raising it with just enough tension to put the fibers on a stretch. All the right hand does is snip with the tip of the scissors the fine, but strong, web-like strands.

There is no room in vascular surgery for blunt dissection. Trying to free the ductus by separating the adventitial strands with a blunt curved forceps will lead

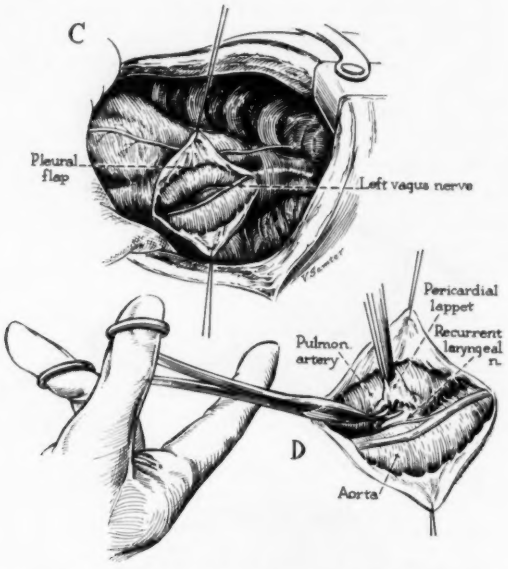

Fig. 2.—*C*, recurrent laryngeal nerve arising from the vagus invariably curves around the ductus and is an infallible guide to its inferior wall. *D*, ductus is freed entirely by sharp dissection (see text).

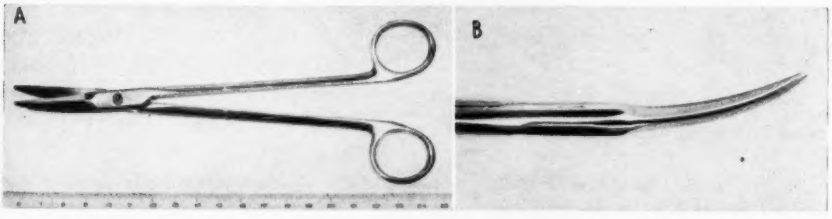

Fig. 3.—Long-handled Mentzenbaum scissors ground down until the blades are very thin are used for sharp dissection in all cardiovascular work.

to catastrophe. The fibrous tissue is stronger than the wall of the ductus, and, as the blunt instrument is being opened to free this tissue, the wall of the ductus will tear. I know because I twice had bleeding occur because of doing this maneuver with a curved blunt cystic duct forceps. Another dangerous instrument used for freeing the ductus or other large vessels is the so-called gauze dissector. It should

be called the "vessel tearer." The small wad of gauze grasped between the tips of a hemostat has at times been used to separate vessels from surrounding tissue. There is no more dangerous instrument around large vessels. The small hard piece of gauze easily rubs away the tough adventitia and tears a hole in the media. Those who have used it know the results.

After the pericardial lappet is dissected free well on the pulmonary artery, the loose tissue superior and inferior to the ductus is cut in similar fashion—always picking up the loose tissue with the forceps in the left hand and gently snipping the strands with the scissors. I apologize for this obvious statement, but occasionally, it is appropriate. Always see exactly where the tip of the scissors is and what it is about to cut. One recurrent laryngeal nerve was severed because this was forgotten.

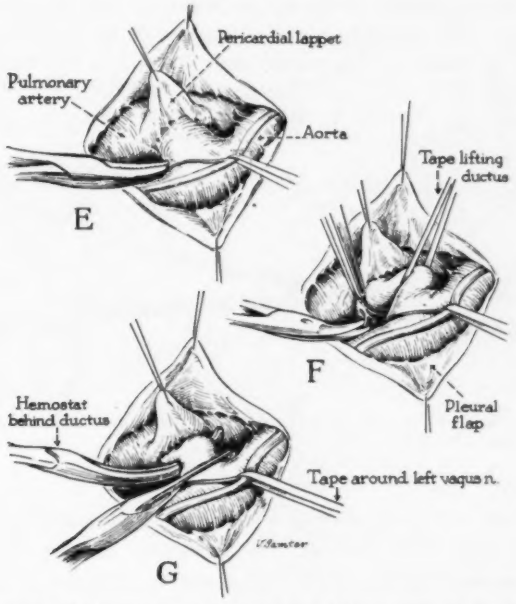

Fig. 4.—*E*, after the visible portion of the ductus has been cleared, a curved cystic duct clamp is gently eased behind the ductus. *F*, while the ductus is elevated by traction on umbilical tape, fibrous tissue connections on the posterior surface are thoroughly freed. *G*, slight traction is made on the ductus to facilitate placement of the toothed clamp on the aortic side of the ductus.

After the visible portion of the ductus has been cleared, a curved clamp is worked behind the ductus (Fig. 4*E*). As it is carefully moved from below upward, one watches for the tip of the clamp. Its points must be recognizable through the fibrous tissue being pushed ahead of the clamp. If one cannot see an outline of the tip of the clamp, one may be pushing against the wall of the ductus and should withdraw and try again at a slightly different angle. When the points of the forceps can be identified, they may be opened a bit and the fibrous tissue cut with a scissors. A piece of umbilical tape is then drawn beneath the ductus to hold it up

while further dissection is carried on. It is of the greatest importance to pick up and cut strands of tissue on the posterior wall of the ductus on both its pulmonary and its aortic end (Fig. 4*F*). It is amazing to see how a ductus, which appears to be a direct fistula between the aortic and the pulmonary artery, lengthens when the fibrous tissue holding it to surrounding structures is cut away. Removal of all loose tissue is important to lengthen the ductus: It is imperative or the clamp will slip. The teeth in the clamp are obviously very short (Fig. 5). If all the loose tissue and, especially, the pericardium are not completely removed from the ductus, the teeth will bury themselves in this loose tissue and allow the stump of the elastic ductus to slip from between the jaws.

The angled serrated clamp is now applied to the aortic end of the ductus crowding onto the aorta if the ductus is short (Fig. 4*G*). As the pulmonary end of the ductus is clamped, a thin hockey-stick type retractor [1] is used to put the pulmonary end of the ductus on a slight stretch and to hold away any loose tissue behind the ductus (Fig. 6*H*). One must be absolutely sure that the ductus, and it alone, is in the jaws of the clamp. With a long straight scissors the ductus is cut. The aortic end is sutured first. No. 5-O Deknatel nonabsorbable surgical suture material (silk) on a curved No. 9 needle is routinely used. A suture is begun at the lower

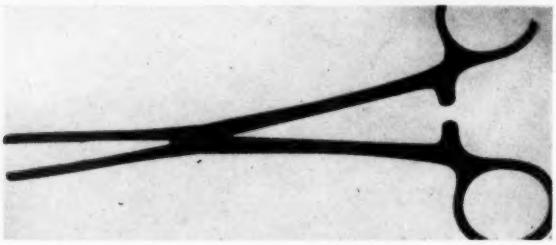

Fig. 5.—X-ray silhouette of a ductus forceps or clamp which illustrates the principle of tiny teeth in the opposing jaws.

angle of the aortic stump, tied, and continued upward as a to-and-fro basting suture placed distal to the clamp and always carefully guided through all the layers of tissue. Better occlusion is obtained if all stitches are placed on an even line, and this can be accomplished if the curved needle is always guided in the slight hollow of the occluded ductus clamp. After completion of this suture, the end is held taut and a second stitch is placed and tied in the proximal end of the aortic stump of the ductus (Fig. 6*I*). The short end of this stitch is tied to the end of the previously placed stitch. A continuous row of over-and-over stitches is then placed distal to the first row, and the end is tied to the end of the original suture. By using two sutures, i.e., tying the first to the anchored second stitch, bleeding due to loosening of the suture is averted when the clamp is removed. Placing the top rows of sutures at different levels likewise lessens bleeding. The ends of the sutures are not cut but held up taut in one hand as the clamp is partially released to allow blood to enter the needle holes and the suture line. The clamp is closed to the

1. This and other instruments illustrated in this paper are manufactured by Bruno Richter & Co., 843 Duane Ave., Glen Ellyn, Ill.

second notch and used to retract gently the aorta while the pulmonary end of the ductus is being sewn. The pulmonary end of the ductus is sutured in a similar manner, except that one suture is used for both rows of stitches. The clamp on the pulmonary end of the ductus is opened and removed first, then the clamp on the aortic end. In each instance, by holding the ends of the tied sutures taut as the clamp is being cautiously opened, the stump of the ductus is kept between the jaws of the clamp and can be occluded in case hemorrhage from the suture line necessitates a few extra stitches.

The following variation in technique gives added safety when operating upon unusually large or especially short ducti, ducti that have been previously operated upon unsuccessfully, ducti that have been affected by endarteritis, and ducti that have associated pathology, such as an aneurysmal dilatation, in fact, any ductus

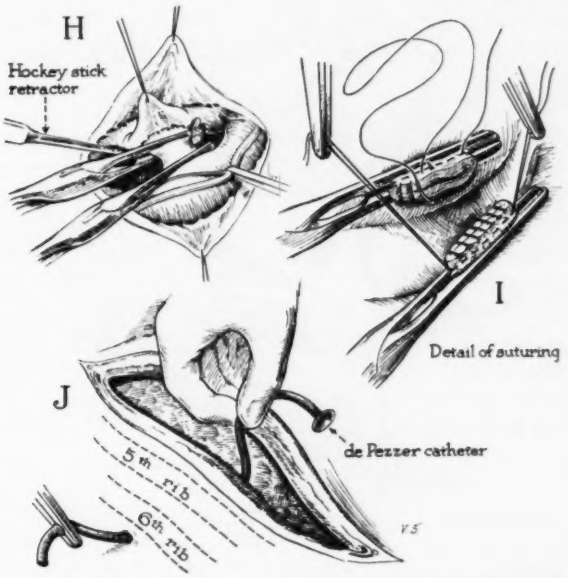

Fig. 6.—*H*, with a specially made hockey-stick retractor, all loose tissue and the edges of the pericardial sac are held away while the pulmonary end of the ductus is clamped. *I*, the sutures, always of 5-0 silk, are placed about 1mm. apart. *J*, the chest is always drained.

which at the beginning of the dissection does not appear to be rather standard in size, shape, and appearance (Fig. 7*K*).

The parietal pleura is opened as before but is dissected from the lateral surface of the aorta just below the origin of the left subclavian artery. The aorta, lateral to the origin of the ductus, is dissected from its bed and the necessary intercostals are doubly ligated and cut to allow application of the Potts-Smith aortic clamp. The aortic clamp may or may not be completely closed according to local conditions while the ductus is being dissected from surrounding structures. After it is completely freed, the aortic clamp is closed and a ductus clamp is applied to the pulmonary end of the ductus. The fact that the aortic end of the ductus is

occluded in one plane and the pulmonary end in another plane raises no technical difficulties with either cutting or sewing the ductus. The technique of suture is the same as that previously described.

Regardless of the technique used, it has been our routine to place a piece of Gelfoam between the sutured ends of the ductus. No case of postoperative hemorrhage has occurred, and we are loathe to discontinue a custom probably having no virtue to support it.

The posterior parietal pleura is closed with interrupted sutures.

A dePezzer catheter with all but a flange removed is drawn through a small stab wound through the sixth interspace from the inside out (Fig. 6*J*). The drain is later connected with a water-seal bottle and is left in the chest about 48 hours. We will not be dissuaded from draining the chest after all ductus operations be-

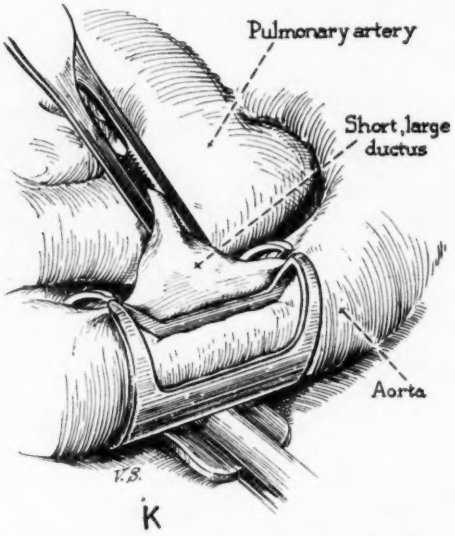

Fig. 7.—*K*, in case the ductus is short, large, or in any way difficult to expose, the aortic clamp is applied for safety.

cause no complications have arisen from its use, and we have had to do a thoracentesis after only 1 of 214 operations and that for a late accumulation of fluid following atelectasis.

The chest is closed with absorbable surgical (gut) suture material, not because we prefer it to silk, but because we believe the operating time saved by closure with surgical gut more than offsets the scanty virtues of closure with silk or cotton. The ribs are apposed with two heavy sutures placed about the adjoining ribs beneath the periosteum. A running stitch in the intercostal muscles and the periosteum completes close apposition of the ribs. The muscles and subcutaneous tissues are closed with running sutures of 3-0 or 4-0 surgical gut. The skin is closed with running silk sutures.

POSTOPERATIVE CARE

Every patient is given 300,000 units of penicillin every day for approximately one week after operation—another custom which may be questionable. The intravenous polyethylene tube is left in the ankle 24 to 48 hours. After this tube and the chest drain have been removed, the child is allowed to sit up and get up as he wishes.

Postoperative complications have not been troublesome. In a previous publication we referred to the distressing complication of severe tracheobronchitis, which occurred in three cases and necessitated tracheotomy in one. Since that time in over 150 cases no tracheotomies have been necessary, owing no doubt to greater skill of the anesthesiologist in choosing exactly the right size intratracheal tube and to added dexterity in its insertion. The occasional case of atelectasis has cleared spontaneously without further trouble. Minimal complications, such as thrombophlebitis from the intravenous tube, upper respiratory infections, abdominal distention, mild bronchitis, and occasional stitch abscess, etc., are annoying but not serious.

MORTALITY

There has been no mortality in this complete consecutive series of 214 patent ducti operated upon at Children's Memorial Hospital. The reasons for this good fortune are several. First, these operations have all been performed on children up to 15 years of age. The operation is far simpler to do in patients aged 5 than aged 15 and, again, far simpler in those aged 15 than 25 or, especially, 35. The second is skillful administration of anesthesia. The third is excellent postoperative care by residents and nurses. The fourth is just plain good luck.

Operative correction of the uncomplicated patent ductus arteriosus has become an extremely satisfactory operation. One can truthfully tell the parents that their child has an excellent chance of surviving surgery and that after operation the child will have a normal heart and can run and play like other healthy children

707 W. Fullerton Ave.

DISCUSSION

ON PAPERS BY DRS. SCHMITZ, SAUVAGE, KANAR, AND HARKINS AND DR. POTTS

DR. CARL DAVIS JR., Chicago: In discussing the excellent presentation of Dr. Potts on the technique of surgical correction of the patent ductus arteriosus, one must congratulate him on the outstanding results in a large series of cases without a single fatality.

At the Presbyterian and Cook County Hospitals, in our limited experience with patent ductus arteriosus, Dr. E. H. Fell and I have encountered some interesting problems. In a series of approximately 50 patients, there have been 11 adults, ranging between the ages of 20 to 36 years. Infants and children, 1 to 18 years of age, comprise the rest of the group. Surgery of the ductus has proved to be more formidable in the adult group. In two instances of surgery of coarctation of the aorta, a patent ductus was divided. Two adult cases were complicated by bacterial endarteritis. There has been one fatality in the entire series—a 35-year-old man who failed to survive an uncontrolled hemorrhage at the time of dissection of a short friable ductus.

(Slide) This illustration shows the techniques used in this series of patients. The multiple suture ligature technique, as advocated by Dr. Blalock, was employed in about 10 patients. There were two instances of recurrence of the continuous murmur, three days and two months after surgery, respectively, raising the question as to whether the ligatures cut through the ductus and a portion of the shunt was reestablished, or whether the ligatures were not tied tightly enough to occlude the ductus completely. The ductus was divided between Potts clamps in approximately 25 patients. The Potts-Smith aortic clamp proved of value in four cases with a short broad ductus.

(Slide) This drawing shows the findings at a second operation (performed approximately one and one-half years after the first) in a 7-year-old girl who had recurrence of the ductus murmur two months after multiple suture ligatures were used to close the ductus. Actually, at operation the nonabsorbable surgical sutures (silk) seemed displaced to the aortic end of the ductus.

(Slide) Because of the indurated tissues and the risk of hemorrhage the Potts-Smith aortic clamp was employed on the aortic end of the ductus and the Potts ductus clamp on the pulmonary end. Two rows of 5-0 silk were used to advantage—one a deep row of running mattress sutures and a second outer row of running over-and-over sutures to insure a sale closure.

(Slide) In the preoperative roentgenogram note the enlargement of the heart, the prominence of the pulmonary conus, and the increased vascular markings of the lung fields. In the postoperative roentgenogram, taken four minutes after the division of the ductus, there is obvious improvement in the lung fields, as well as a marked decrease in the size of the heart.

I should like to emphasize that the correction of the patent ductus arteriosus in adults is far more hazardous and offers greater technical problems than in children. Early surgery of the patent ductus arteriosus is advised.

Personally, I like the technique of Dr. Potts, for it is very gratifying to be able to tell the parents that the patent ductus is corrected and that in the future their child should be able to undertake normal activities without concern to his heart.

DR. JOHN GRINDLAY, Rochester, Minn.: Studies, such as the excellent one presented by Dr. Harkins today—experimental studies on dogs and pigs—have certainly convinced most of us that the arterial homograft is inferior to the autograft. We have read papers recently showing that arterial homografts undergo late changes, essentially a progressive degeneration. It is unfortunate that we don't have arterial autografts available for bridging gaps in major arteries.

I am certain Dr. Harkins and his associates would agree that if we could find a vein more accessible and less important than the inferior vena cava which would suffice for an autograft in a major artery it would be a distinct advantage.

Two years ago I began a study in dogs in which the gap in the aorta, after resection of the portion between the renal arteries and bifurcation, was bridged with a segment of the external jugular vein of the dog. Of course, this thin-walled vein would have dilated tremendously and would certainly have ruptured in a short time, if not immediately. To prevent dilatation and rupture the segment of external jugular vein was placed inside a tube of Ivalon sponge. This is a wettable, nonirritating, sponge-like material which acts merely as a skeleton for the fibrous tissue which invades it from surrounding tissues. Most of the dogs were killed about a year after the procedure was performed, and in all of them the lumen of the graft was that of the aorta above the graft.

To accomplish this anastomosis, I turned the vein and surrounding tube back at each end of the graft so that a cuff was formed and sutured the edge of the cuff to the edge of the aorta at either end. The cuff was then turned over, so that, in effect, there was a broad zone in which union of the graft and the aorta could occur, not merely the line of anastomosis. I think this technique contributed greatly to the success of the experiments.

Tubes which were not lined by vein grafts were used in other dogs. The tubes remained patent for many months, although at nine months all but a few of them were completely occluded. Unlined tubes, of course, had to be made leakproof with a coating of polymerized gelatin, a form of gelatin which is absorbed very slowly.

DR. JOHN JONES, Los Angeles: I have nothing but praise for Dr. Potts, and I agree with everything he had to say. I should like to add a point or two that may be of some help to the casual operator in this field of division of the patent ductus arteriosus.

We have a regular routine operation for patent ductus arteriosus, and it is done in steps. First, none of the dissection is done blindly. In order to be sure that one is not dissecting blindly, one obviously has to have good exposure. I think a most adequate exposure is the posterolateral approach for this operation, just as it is in the resection of a coarctation.

We have learned through the years that the surgeon can get into trouble with dissection of the patent ductus areriosus, regardless of how many patients he has operated upon. For that reason we have long since gone to the procedure, first of all, of mobilizing the aorta above and below the patent ductus arteriosus before the ductus is palpated and before it is dissected at all.

There is one way to get into difficulty and that is trying to divide a ductus that has not been dissected out. It is a matter of only three or four minutes of work to mobilize the aorta above and below the ductus, pass a Penrose drain around the aorta above and below, and then, with gentle traction on the two Penrose drains, use Dr. Potts's method of sharp dissection of the areolar tissue and the lapel of the pericardium that comes over the ductus.

In other words, I believe there is no patent ductus arteriosus that cannot be divided in one way or another.

With that method, the operation is very simple to perform in children; in an adult, however, one may encounter an extremely short patent ductus, and that presents another problem. I have used the Potts aortic clamp on the aorta side and the Potts ductus clamp on the pulmonary side, and that works out all right in children. On the other hand, when one is doing this procedure on a number of adults, 25, 30, or even 35 years old (and we have done it on patients who were 45 years old), one is bound to encounter arteriosclerotic changes at the site of the junction of the patent ductus and the aorta itself, and certainly it is not safe to place even a Potts aortic clamp on that type of vessel.

Therefore, in the adult, when we find a short patent ductus, we first mobilize the aorta, just as we would to divide it, as Dr. Potts has shown here, with the Potts clamps, but after the Penrose drains are placed around the aorta we dissect what we can of a short patent ductus; we avert traumatizing the aorta at the site of its junction with the patent ductus, and then, with everything all set, a clamp is placed upon the aorta above the ductus, the second clamp is placed upon the pulmonary side of the ductus, and the third clamp is placed on the aorta just below the ductus. Then we cut the ductus flush with the aorta and usually see there the arteriosclerotic plaque and the arteriosclerotic changes that invariably will cause trouble if an attempt is made to divide the ductus between just the two clamps.

We then quickly proceed to repair the hole in the aorta so that the clamps can be removed in 15 or 20 minutes, and then the pulmonary side of the ductus can be closed at leisure.

These tricks we have learned the hard way. Some of our patients have had hemorrhages, and so on. If there is any question that a ductus is too short, either the operator has failed to do an adequate dissection of the ductus—and if he does not dissect it well the clamps will slip off the aorta—or, in the case of an adult who has sclerotic changes, the clamp may go directly through the vessel, and there will be bleeding.

We know that regardless of what might happen, if the aorta is mobilized above and below the ductus, one can never get into trouble that one can't get out of.

LATE PERIPHERAL ARTERIAL EMBOLECTOMY

JOHN H. OLWIN, M.D.
W. S. DYE, M.D.
AND
ORMAND C. JULIAN, M.D.
CHICAGO

UNDOUBTEDLY a major factor in success or failure in peripheral arterial embolectomy has been the time elapsing between the occurrence of the embolism and surgery. There is no uniform agreement on the limits of the optimum period for embolectomy. McClure and Harkins [1] set the first 12 hours as the optimum period. Heanley [2] would have the surgery done in the first 10 hours. Pearse,[3] in reviewing 282 embolectomies, found little difference between the results of those done in the first and those done in the second five-hour periods. The combined average of successful operations in these two periods was 40. The average of the second 10-hour period was 14%, and of the third was 8%. He concluded that after 48 hours the operation was not worth doing. He attributes failure to (1) the formation of a thrombus distal to the embolus, so-called "tail thrombus," and (2) changes in the intima. Of four successful embolectomies reported by Danzis,[4] two were done 12 to 16 hours, one, 16 to 20 hours, and one, 24 to 48 hours after embolism. Lund [5] reported that in 27 embolectomies none was successful when done after nine hours. Linton [6] believes that most failures are due to the formation of a secondary thrombus distal to the embolus, particularly in the smaller tributaries where the clots cannot be removed, and urges embolectomy in the first six hours. de Takats [7] states that, statistically, 40% of the cases show restoration of blood flow if the embolectomy is done in the first 10 hours. Embolectomy, then, is a procedure of the greatest urgency, and a delay of an hour may mean the difference between success and failure.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

The opinions expressed here are those of the authors and not necessarily those of the authorities of the Veterans Administration.

From the Department of Surgery of the Veterans Administration Hospital, Hines, Ill., the Presbyterian Hospital of the City of Chicago and the Chicago Memorial Hospital.

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There are, however, some patients who, for various reasons, do not undergo embolectomy during the optimal period but in whom immediate progressive changes of the affected part do not develop. It would appear that the collateral circulation in these patients is adequate to supply nutritional needs. Even though life and limb may not be lost, there is usually impairment of function. Numbness, paresthesias, lowered temperature, weakness, and claudication are frequent complaints. Examination may reveal absent pulses, and normal or partially altered temperature, color, and sudomotor reactions. Trophic changes are usually not present. Oscillometric readings are reduced or absent. The usual treatment for these limbs has been sympathectomy. Vasodilating drugs have also been used, and in some instances continuous anticoagulant therapy. All treatments fall short of the desired objective—the restoration of normal sensation and function.

It is the purpose of this paper to present six patients who have been operated upon after the optimum period for embolectomy had passed and in whom the flow was reestablished in the obstructed vessel. Two of these patients were operated upon at 22 and 24 hours respectively, only hours after the presently accepted optimum period. Four underwent surgery from four days to three and a half months after embolism.

CASE REPORTS

CASE 1.—M. C., a 46-year-old white woman, entered the Chicago Memorial Hospital on Nov. 4, 1952, with a history of sudden onset of coldness of both legs and inability to move the left foot. This had occurred at 6:00 a. m. on Nov. 3. The patient gave a history of coronary occlusion three years earlier, as a child had had rheumatic fever, and in the last three years had been given digitalis intermittently.

On admission her blood pressure was 138/100, and auricular fibrillation was present. The liver was palpable 4 cm. below the right costal margin. The left lower extremity was cold distally from a point 4 in. (10.2 cm.) below the knee and was mottled in appearance, and the patient could not move the left foot. The left femoral pulse was absent. On the right, the foot was cold, but motion and sensation were present. The right femoral pulse was palpable to an inch (2.5 cm.) below the inguinal ligament. A preoperative diagnosis was made of bilateral common femoral embolism with possible extension into the iliac on the left.

The patient was taken to surgery approximately 22 hours after the onset of symptoms, and under spinal anesthesia simultaneous incisions were made over the bifurcation of the femoral arteries. A partially organized thrombus was removed from the bifurcation of the femoral artery on both sides, along with a "tail thrombus" in each instance. The arteriotomy incisions were closed, and pulses were observed in the artery exposed. Immediately after surgery both feet were warm, but no pulses were felt. Heparin was used postoperatively.

Two days following surgery the dorsalis pedis pulse could be palpated bilaterally. Both pulses remained palpable, and on Nov. 28 the patient was walking without abnormal signs or symptoms. She is being considered for mitral commissurotomy.

CASE 2.—J. E., a 63-year-old white man, entered the Chicago Memorial Hospital on Feb. 13, 1951, with a history of sudden onset of severe pain in the right foot 20 hours earlier. He immersed it in hot water without relief, and the pain soon progressed to the knee. Numbness and weakness of the foot and lower leg developed shortly thereafter.

On admission the patient's pulse was 80, full and regular. An electrocardiogram showed myocardial damage, but definite evidence of infarction was not present. The right leg from the knee down was pale, cool, and partly anesthetic. The popliteal, dorsalis pedis, and posterior tibial pulses were absent on the right. There were no pulses in the left foot. A diagnosis of generalized arteriosclerosis with right femoral arterial embolism was made, and the right femoral artery was explored 24 hours after the onset of symptoms.

A large, partly organized thrombus was removed from the bifurcation of the femoral artery. With the aspirating tip a "tail thrombus," extending the length of the superficial femoral artery and apparently to below the knee in the popliteal, was removed (Fig. 1). After closure of the

longitudinal incision in the common femoral artery a pulse was observed in the 8 cm. of artery exposed and a popliteal pulse was palpable after surgery. Heparin was used preoperatively, and postoperatively.

Six hours after surgery bleeding from the wound site was apparent, and a hematoma was noted. Despite this, heparin was continued. The bleeding lessened and finally stopped about 48 hours after surgery. The medial aspect of the right thigh was swollen and indurated from the hematoma. Three days later the swelling was less, but numbness and anesthesia persisted, and the leg at this point was obviously nonviable. Edema then developed in the other leg. From this point uremia slowly developed. The patient became disorientated on March 2, and died on March 7, three weeks after the embolectomy.

It is considered possible that the perfusing of a questionably viable limb by the restoration of arterial flow may have contributed to or even been responsible for the uremia, which may have developed on the basis of absorption of toxic materials.

CASE 3.—H. G., a 57-year-old man, entered the Chicago Memorial Hospital on Jan. 22, 1951. Three years prior to admission he had apparently had a pulmonary embolism with hemoptysis and at the same time a small left popliteal embolus. The numbness and pallor of the foot disappeared after the patient was placed on bishydroxycoumarin (dicumarol®) therapy. Four days prior to admission the patient noticed a slowly developing numbness, coldness, and weakness of

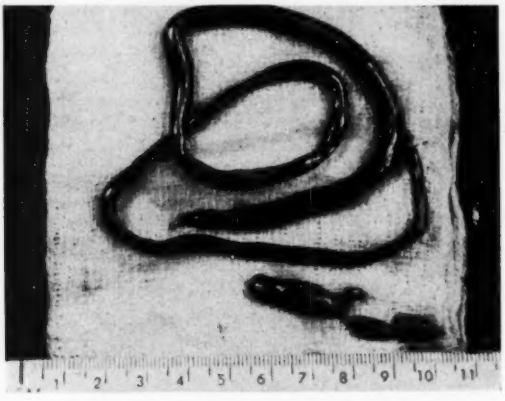

Fig. 1 (Case 2).—Clots removed from the right femoral and popliteal arteries. The smaller fragments are the partially organized embolus removed from the femoral bifurcation, and the worm-like clot is the "tail thrombus" which extended from the femoral bifurcation to below the knee in the popliteal artery.

his right leg and foot. The following day the foot was waxy in color and on Jan. 20, two days prior to admission, the foot was entirely without feeling and motion was painful. This condition persisted to the time of admission.

Examination revealed pulses to be present and normal in the left foot and leg but absent below the femoral on the right. The right foot and lower third of the lower leg were pale, cool, and anesthetic. Movement of the foot was painful. The pulse was regular, there was a systolic murmur at the apex transmitted to the precordium, and the blood pressure was 118/68.

A diagnosis of right popliteal embolism was made, though a primary thrombosis could not be ruled out. The right popliteal artery was explored on admission, four days after onset of symptoms, and for a distance of 7 cm. no pulse was seen or felt. The artery was firm throughout this distance. Through a 1.5-cm. longitudinal incision an old but nonadherent clot and several soft fragments of recent thrombus were removed, along with some atheromatous material. Free arterial bleeding was then obtained. It was obvious at this point that the obstruction was on the basis of embolism. Heparin was injected locally, and after closure of the artery a pulse was present. Postoperatively the popliteal, dorsalis pedis, and posterior tibial pulses were palpable in both legs, though less forceful on the right. Because of continued pain and numbness over the lateral aspect of the foot, a right lumbar sympathectomy was done on Feb. 5, 1952. When the

patient was discharged, on March 4, 1952, the numbness had disappeared, pulses were present in the right foot, the color and temperature of the leg and foot were normal, and he was walking without claudication or other pain.

CASE 4.—F. H., a 60-year-old fireman, was admitted to the Veterans' Administration Hospital, Hines, Ill., on Jan. 3, 1952, with a history of the onset of sudden agonizing pain in the left arm on Dec. 29, 1951. This came on 15 minutes after a prolonged period of snow shoveling. Moments later the forearm and fingers became blue and cold, and the patient was unable to move his fingers. About 30 minutes later he fainted, and he was unconscious for five minutes. The pain gradually disappeared, and the color, temperature, and movement of the forearm and fingers steadily improved for three days. There was no history of heart disease.

Physical examination revealed a blood pressure of 140/86 and a pulse rate of 88 with normal rhythm. The left arm below the elbow was cyanotic and cold. The axillary pulse was palpable, but the brachial, radial, and ulnar pulses were absent. There was a normal range of motion of the arm and fingers though the strength was impaired. Sensations of touch and pain were absent in the hand. An electrocardiogram showed "possible left stain" and myocardial damage. Infarction could not be ruled out.

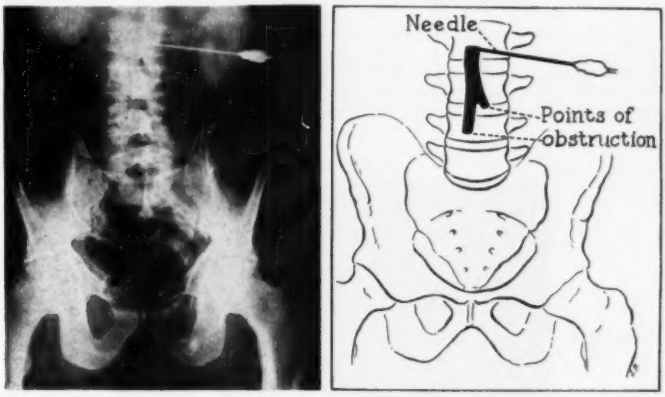

Fig. 2 (Case 5).—Block in both common iliac arteries just below the aortic bifurcation. On the left is the aortogram proper, in which the lower aorta is poorly outlined. On the right the aortogram is interpreted in line drawing. At this time, April 14, 1952, the aortic bifurcation was still open.

Diagnosis of axillary arterial embolism was made, and on Jan. 4, 1952, six days after its occurrence, a large embolus was removed in retrograde fashion from the axillary artery along with a 7-cm. "tail thrombus." There was considerable periarterial reaction in the area of the obstruction. The arm and hand were warm and pink in the immediate postoperative period, though the radial and ulnar pulses were not palpable. Heparin was given postoperatively. The following day the brachial pulse was present to the elbow, the pulses below still being absent. At the time of the patient's discharge, on Feb. 29, 1952, strength and sensation of the limb were normal except for numbness of the thumb and forefinger tips. On Nov. 21, 1952, the radial pulse was palpable, and the numbness had disappeared.

CASE 5.—E. S., a 44-year-old Negro clerk, had had a known rheumatic heart disease with mitral stenosis and auricular fibrillation for some years. He had been reasonably well, carrying on his usual work until 19 days prior to his admission (March 10, 1952), when he apparently suffered a mild cerebral embolus. The history is not clear during these 19 days, but, since on his admission the pulses were absent in the left groin, knee, and foot, and from the popliteal pulse down on the right, it was assumed that emboli had formed in the left common or the external iliac artery and the right popliteal or superficial femoral at the time of or subsequent to his cerebral embolism. At the time of his transfer to the Vascular Service, on April 4, 1952, the above situation obtained, and there were ischemic ulcers over the plantar surfaces of the first and third toes

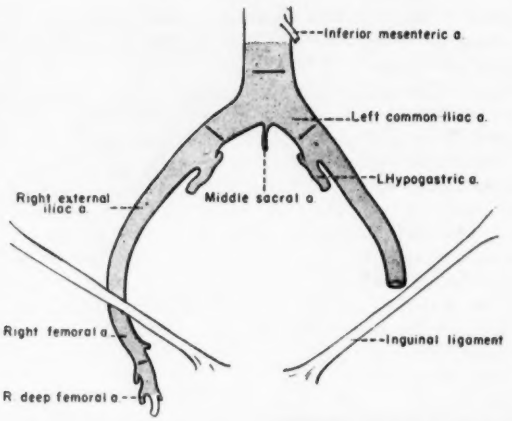

Fig. 3 (Case 5).—Schematic drawing representing the occluded area of the great vessels found at the time of surgery, June 9, 1952, eight weeks after the aortogram shown in Figure 2. The lines of surgical incision are shown just above the aortic bifurcation, just above each common iliac bifurcation, and just proximal to the right femoral bifurcation. The clot extended from the lower abdominal aorta throughout the main iliac arteries and to the femoral bifurcation on the right.

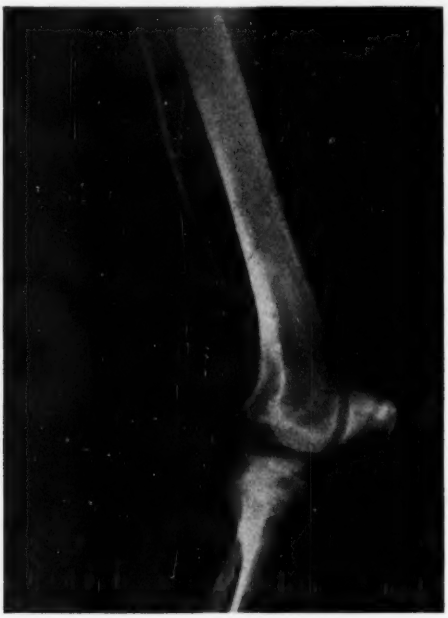

Fig. 4 (Case 5).—Arteriogram made after the great vessels had been successfully cleared, showing the obstruction in the left popliteal artery in its proximal portion. It was cleared of thrombus surgically, but the blocked posterior tibial artery could not be opened completely. The foot and lower leg slowly deteriorated, and amputation had to be carried out below the knee.

on the left. The condition of the left leg and foot deteriorated, the right femoral pulse gradually disappeared, and on April 14 an aortogram showed a block of both common iliac arteries just below the aortic bifurcation (Fig. 2). On May 5, the left leg was amputated above the knee. On June 9, 1952, the pelvic vessels and abdominal aorta were explored up to the origin of the inferior mesenteric artery through a left retroperitoneal approach, and the right femoral artery through an incision over the right upper thigh. Old, well-organized thrombi were removed from the abdominal aorta from a point centrally just below the origin of the inferior mesenteric artery and peripherally through the entire length of both common iliac arteries. The left internal and exter-

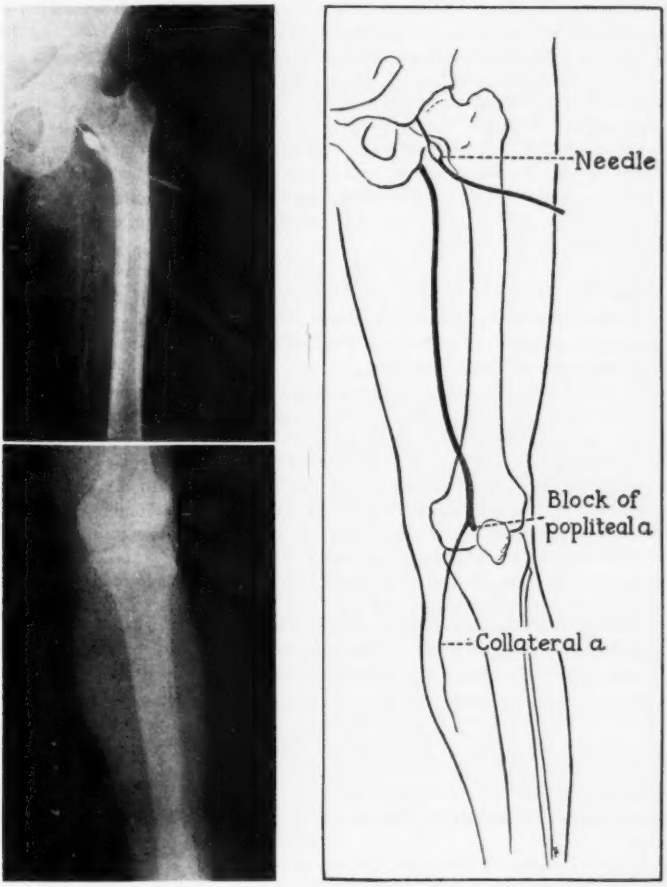

Fig. 5 (Case 6).—Right femoral arteriogram taken preoperatively, showing a block in the midportion of the popliteal artery. This was confirmed at the time of surgery, and the clot was found to extend the entire length of the posterior tibial artery. Because of a low concentration of dye in the vessel and the interposition of the femur, the popliteal artery is seen with difficulty. On the right the schematic interpretation of the arteriogram shows the point of obstruction and a collateral vessel arising just above it.

nal iliac arteries were aspirated, and a moderate retrograde flow was obtained. The external iliac was opened for a distance of 10 cm. The right external iliac artery was cleared of organized thrombus through incisions in the right common iliac and right common femoral arteries. There was no thrombus in either the deep or the superficial femoral artery on the right. This suggested an embolus in the right femoral bifurcation, but the absence of a "tail thrombus" and the presence

of the right femoral pulse at the time of admission, with its gradual disappearance, are more suggestive of a retrograde thrombosis from the left common iliac to the aortic bifurcation and subsequent extension to the right iliac and femoral vessels. This view is further supported by the findings of an open aorta to the bifurcation on aortography, April 14, and a completely blocked aorta to just below the origin of the inferior mesenteric artery at surgery nearly two months later. After surgery both femoral pulses were palpable. The right popliteal was not present. A femoral arteriogram on June 26, 1952, showed open femoral vessels, but obstruction from the beginning of the popliteal artery. On June 30, 1952, the right popliteal artery was explored, and an old organized thrombus was removed for a distance of 10 cm. above the bifurcation of that artery. The posterior tibial artery was opened at the ankle, and a ureteral catheter was passed from above and below to a point of obstruction about midway between knee and ankle. This obstructed segment was about 5 cm. in length and could not be cleared from either above or below. It was not considered worth while to open the artery at the midpoint.

Postoperatively the popliteal pulse was palpable. The lower leg remained cold and pulseless, however, and despite a lumbar sympathectomy on July 30, 1952, dry gangrene of the foot developed, and on Aug. 23, 1952, the leg was amputated below the knee. Because of the patient's poor cardiac condition, he was not fitted with prostheses. It was considered probable that the earlier thrombectomy of the aorta and the iliac and femoral vessels on the right made possible the saving of the knee joint in this case. The possible role of thrombectomy in the patient's survival is, of course, pure conjecture.

CASE 6.—E. M., a 31-year-old white man, was admitted to the Veterans Administration Hospital, Hines, Ill., on March 3, 1952, complaining of pain in the left calf for three days. He was known to have an old rheumatic heart disease with mitral stenosis and auricular fibrillation and had been in the hospital in December of 1948 because of right posterior tibial embolism for which a sympathectomy had been performed.

He was in a mild state of cardiac decompensation, and the left foot and lower leg were pale and cold. There was no pulse below the femoral. Lumbar sympathetic block was performed, and the foot became warm. A left femoral arteriogram on April 4, 1952, showed open femoral vessels but a block in the midportion of the popliteal to its bifurcation (Fig. 5).

Mitral commissurotomy was carried out on April 10, 1952, with marked improvement of cardiac symptoms. The patient's chief complaint at this point was cramping pain in the left calf when he tried to move about. The nutrition of the leg and foot remained satisfactory. The popliteal, dorsalis pedis, and posterior tibial pulses were not palpable on the left. On June 2, 1952, three months after the onset of symptoms in the left leg, embolectomy and thrombectomy were carried out on the left popliteal and posterior tibial arteries. Eight centimeters of the popliteal artery was found to contain an organized thrombus, which extended into the posterior tibial and possibly the anterior tibial for an undetermined distance. Through two transverse incisions, 2 and 6 cm. respectively above the bifurcation of the popliteal artery, the clot was removed down to 1.5 cm. inside the posterior tibial artery. Through an incision in the latter at the ankle further thrombectomy was done by passing a ureteral catheter from above and below through the lumen of the artery. A good pulsatile flow was obtained, and heparin was instilled intra-arterially as all incisions were closed. Heparin was continued until the effects of ethyl biscoumacetate (tromexan®) were adequate, the latter drug being continued indefinitely because of the persistent auricular fibrillation. Because of such therapy postoperative arteriography has not been done.

All pulses were present after surgery, and the patient was able to walk a half mile without claudication. When last seen on Nov. 21, he was free from symptoms, and popliteal and dorsal pedal pulses were present.

COMMENT

Successful embolectomies after the optimal period has elapsed are dependent upon an undisturbed collateral circulation adequate to provide basal nutrition to the affected part. Various factors may encourage or discourage this collateral supply. The degree of spasm and the methods utilized to relieve it, and the use of anticoagulants are two of the major influences. These factors may to some extent also affect the status of the occluded vessel and its branches.

The emphasis of this paper is on those patients who obviously have adequate circulation for proper nutrition of the member but who require further blood supply for proper function and sensation. In our hands sympathectomy has rarely restored these to normal. It remains then to reopen the blocked main arterial channel, and if possible its branches, if this is to be accomplished. Fortunately many of the small branches of the collateral circulation remain open up to the blocked main channel and are ready to carry blood once that channel is reopened. The extent of these collateral vessels, as well as the exact site of block, may be determined by arteriography. Such examination may also reveal the presence or absence of a segment of open vessel below the embolus and accompanying thrombus. Both of these points of information are helpful in planning the embolectomy, particularly in the late cases.

The time limits of successful embolectomy and thrombectomy are still poorly defined. The factors setting these limits are only partially understood. Organization of the clot, atheromatous changes in the intima before the embolism and fibrous changes after it, calcific changes in the media and occasionally the intima, continued arterial spasm, and total volume of patent branches from a main vessel are some of the factors involved. Cases 5 and 6 would indicate that months rather than days or weeks may elapse without irreparable changes in main channel vessels. Case 5 suggests that large vessels may be more amenable to successful thrombectomy than smaller ones. Yet in Case 6 the posterior tibial artery was reopened surgically with apparent good results. The judicious use of anticoagulants undoubtedly plays an important role in the success of this type of surgery. Sympathectomy will undoubtedly often be a necessary adjunct. How long a reopened channel will remain patent is still not known. The rate at which intima re-forms will be an important factor, for surely in some cases the lining intimal cells are irreparably changed. Closely related to this will be the required period for continuing the use of anticoagulants. Some cases, particularly those with persistent auricular fibrillation, may require such therapy indefinitely in order to avoid further emboli.

Case 2 suggests an interesting and difficult problem. Does the opening of a main arterial channel in a questionably viable limb endanger the patient's life by exposing him to absorption of toxic substances from necrotic tissue? Could it be the deciding factor in a patient with an already disturbed body chemistry? The dramatic improvement in the general condition of patients whose gangrenous limbs have been refrigerated would appear to support such a conjecture.

Many more cases are needed before indications for and limitations of late embolectomy can be properly defined. We believe, however, that with careful surgery and the proper use of adjunctive therapy there are many cases in which it may be attempted with little to lose and much to gain.

SUMMARY

Six patients underwent embolectomy with the restoration of blood flow, 22 hours, 24 hours, 4 days, 6 days, 3 months and 3½ months, respectively, after embolism. In four patients the function was restored to normal or near normal. The fifth died in uremia possibly contributed to by the restoration of blood flow to a questionably viable limb. In the sixth patient further thrombotic complications interfered with the restoration of normal function, though there was material improvement in circulation to certain parts.

Implications of the results in these cases are discussed.

AN EVALUATION OF ENDARTERECTOMY

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AND
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LOS ANGELES

THE INTRODUCTION of endarterectomy has provided the surgeon with a tool for direct attack upon arteriosclerotic obstruction of the major arteries. Endarterectomy has been greeted with interest, but some of the original enthusiasm has been tempered by the disappointment associated with unexpected failures.

Experience with this operation at Veterans Administration Hospital has varied from unsatisfactory to extremely good. Because most of the initial failures appeared to have been caused by technical problems or faulty selection of patients it was believed that a review of a series of cases of thrombotic obstruction of major arteries might be of value to others in evaluating endarterectomy and its indications.

Rather than stressing the favorable results, this paper will emphasize the reasons for unsuccessful outcome and will suggest some techniques that may diminish the hazard of failure.

MATERIAL

Forty-three patients who had chronic obstruction of a major artery have been seen in consultation by members of the surgical staff of the peripheral vascular group at Veterans Administration Hospital since July 1, 1950. Diagnosis has been confirmed by arteriography or autopsy in all but one instance. The distribution and extent of the obstructions are summarized in Table 1.

Sixteen of the group of 43 patients were not operated upon, except for two amputations which were done as emergencies. Nine of the 16 were refused as surgical candidates because of a general medical debility, such as severe hypertension, recent coronary thrombosis, recent cerebrovascular thrombosis, or simply diffuse arteriosclerosis. Active pulmonary tuberculosis and inoperable prostatic carcinoma were each considered contraindications in one patient. Two patients had such extensive and rapidly progressive gangrene as to be unfit surgical candidates; one of these two subsequently had a hip disarticulation but died in the postoperative period. In the other patient thrombosis of the renal arteries developed as the thrombotic process ascended his aorta.

Cases in which operation of therapeutic intent and those in which secondary amputations and other procedures were performed are listed in Table 2.

Read (by invitation) at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 4, 1952.

From the Surgical Service, Veterans Administration Center, and the Department of Surgery, University of California School of Medicine at Los Angeles.

Procedures less radical than endarterectomy were performed as initial operations upon 12 patients. In two of these instances the general debility of the patient was responsible for the decision to use a lesser procedure. In the remaining 10 patients endarterectomy would have been undertaken except for the apparently unsatisfactory lower end to the intimal dissection. In only 2 of the latter group of 10 was there any significant benefit from sympathectomy.

Eighteen endarterectomies were performed. Five of these were done early in the series by a technique now believed inadequate. Each of these patients had an iliac or an aortic-iliac obstruction, and an attempt was made to remove this block through transverse incisions proximal to the lower end of the block. Creation of a smooth lower end to the dissection, a point emphasized by dos Santos [1] and by Wylie,[2] is difficult through such an approach. Three patients upon

TABLE 1.—*Distribution and Extent of Obstructions*

Site	No.	Length of Obstruction Cm.
Aortic, aortic-iliac	12	5-30
Iliac	11	2.5-16
Iliac-femoral	4	25-30
Iliac-femoral-popliteal	2	45-50
Femoral, femoral-popliteal	14	12-45

TABLE 2.—*Surgical Procedures Performed*

Sympathectomy alone	16
Endarterectomy without previous sympathectomy	12
Endarterectomy after sympathectomy	5
Embolectomy and endarterectomy	1 *
Exploration of femoral arteries	1
Exploration of popliteal artery and immediate amputation of leg	2
Amputation without other surgical treatment	2
Late amputation after endarterectomy	7
Secondary operation for hemorrhage	2

* This patient underwent exploration of a popliteal obstruction which occurred suddenly six days after a successful femoral endarterectomy. An additional segment of femoral artery was endarterectomized, and what was believed to be an embolus was removed.

whom this technique was used had an unsuccessful removal of the obstruction and resultant thrombosis of the segment. The fourth patient suffered a thrombosis of vessels in the uninvolved leg while the aorta was clamped and subsequently had an amputation of the foot. The originally diseased leg, however, appeared slightly improved. A fifth patient died of hemorrhage from disruption of the aortic suture line.

The remaining patients were operated upon by the technique described by Wylie.[2]

1. dos Santos, J. C.: Note sur la désobstruction des anciennes thromboses arterielles, Presse méd. **57**:544-545, 1949.

2. (*a*) Wylie, E. J.; Kerr, E., and Davies, O.: Experimental and Clinical Experiences with the Use of Fascia Lata Applied as a Graft About Major Arteries After Thrombo-Endarterectomy and Aneurysmorrhaphy, Surg., Gynec. & Obst. **93**:257-272, 1951. (*b*) Wylie, E. J.: Thrombo-endarterectomy for Arteriosclerotic Thrombosis of Major Arteries, Surgery **32**:275-292, 1952.

TABLE 3.—*Summary of Operative Results*

Patient	Age	Sex	Site	Total Length Segment Cm.	Preop. Status	Follow-Up Period Mo.	Postoperative Status
C. L.	43	M	Iliac	16	300 ft.	24	Same
H. T.	60	M	Iliac	8	1 block	22	½ block; thrombosis during operation required amputation of other foot
E. M. U.	45	M	Aortic-iliac	10	¼ block	21	Same
J. A. W.	50	M	Iliac	5	50 ft.	20	200 yd.; subsequent cardiovascular accident, hemiplegia limit activity; no femoral pulse; otherwise same
W. B. F.	55	M	Aortic-iliac	20	1 block	½	Dead; hemorrhage from suture line
C. R. J.	52	M	Iliac femoral	25	Rest pain; gangrene, toes	14	No change; amputation, supracondylar
J. W.	51	F	Iliac-femoral	25	200 ft.	13	"Unlimited activity"
W. H. F.	52	M	Aortic-iliac	45	50 ft.	⅙	PO renal artery thrombosis; thrombosis of superior mesenteric artery at operation treated successfully
I. J.	55	M	Aortic-femoral	60	2 blocks	11	Thrombosis and bilateral amputation, thigh and hip
J. H. S.	57	M	Femoral-popliteal	35	1 block; gangrene of toe	10	Toe healed; 1 mi.
W. B. H.	73	M	Femoral-popliteal	35	100 ft.; rest pain	9	No rest pain; 200 yd.
J. R. L.	58	M	Femoral-popliteal	40	1 block; rest pain	8	Unchanged; below knee amputation
H. C.	60	M	(1) Iliac-popliteal	45	75 ft.	⅕	Warm foot, return of pedal pulses; sudden occlusion at 6 days by embolus from iliac plaque
H. C.	60	M	(2) Popliteal	6	Impending gangrene foot and ankle	1	Spotty gangrene of toes and lower leg skin; wound infection; aneurysm of popliteal artery, with rupture and exsanguination
J. H. R.	41	M	Aortic-iliac	25	200 ft.	8	1000 yd. ("nine holes golf")
G. S. B.	52	M	Femoral-popliteal	40	20 ft.; rest pain	7	Unchanged; amputation, supracondylar
H. H.	49	M	Femoral-popliteal	36	100 ft.	1	Good pulses; leg untested
F. A. D.	57	M	Femoral-popliteal	24	100 ft.	1	Good pulses; leg untested

RESULTS

Table 3 summarizes the endarterectomies performed and the results obtained. Six patients were markedly improved by the operation. The reasons for failure of the operation in the remaining 11 are shown in Table 4.

COMMENT

The complications which may result will be discussed under the following headings: thrombosis, hemorrhage, extensive arteriosclerosis in the distal extremity, and severe diffuse arteriosclerosis.

Thrombosis.—The most important factors in the prevention of thrombosis are the complete removal of obstructing irregularities in the endarterectomized segment and the smooth beveling of the edge of the intima at the lower end of the dissection. The very nature of the disease which allows the development of a plane of dissection beneath the diseased intima allows this plane to extend spontaneously if any disease exists in the remaining intima at the lower edge. This unremoved and thickened intima tends to form a flap which catches the onrushing current of blood and obstructs the vessel (Fig. 1*A*). The best technique to avoid this complication might

TABLE 4.—*Reasons for Unsatisfactory Results Following Endarterectomy*

Failure of endarterectomy	
Thrombosis due to thick intimal flap	5
Thrombosis due to extensive distal obstruction	1
Persistent symptoms due to distal disease	1
Embolism from proximal plaque	1*
Death	
Early dehiscence of suture line in aorta	1
Late rupture of aneurysm in repaired vessel	1*
Thrombosis of renal artery	1

* Successive operations on same patient.

be to extend the dissection beyond all the diseased intima, but the diffuse nature of arteriosclerosis often precludes such a maneuver. Julian [3] has recently described the use of vein grafts to replace similar obstructed arterial segments, and the employment of the full thickness of the arterial wall in the suture line would effectively secure the intimal flap and prevent obstruction. A third technique, which was employed in the latter portion of the current series, is the attachment of this intimal flap to the remaining medial wall by a series of sutures (Fig. 1*B*). This repair is easily accomplished if the arterial incision is extended distally for a short distance past the line of intimal resection. Freeman [4] has mentioned a similar method.

The success of endarterectomy was originally predicated upon the use of heparin. It is on occasion possible to perform a successful endarterectomy without heparin, but its use seems indicated during the first 7 to 10 days before a perfect endothelium has re-formed. Systemic administration of heparin is instituted as soon as the

3. Julian, O. C.; Dye, W. S.; Olwin, J. H., and Jordan, P. H.: Direct Surgery of Arteriosclerosis, Ann. Surg. **136**:459-474, 1952.

4. Freeman, N. E., and Gilfillan, R. S.: Regional Heparinization After Thromboendarterectomy in the Treatment of Obliterative Arterial Disease, Surgery **31**:115-131, 1952.

arterial repair is initiated, and the endarterectomized segment is irrigated with dilute heparin solution before final completion of the suture line in the vessel. Regional heparinization is no longer used.

Severe vasospasm occasionally follows endarterectomy, and it has been felt that sympathectomy should be accomplished as the first stage of the procedure in most instances.

In one instance, irregular proximal plaques were shown at autopsy to be the site of thrombosis and embolus formation (Table 4, footnote). Markedly irregular plaques should be removed from the proximal arterial segment wherever possible, but in most instances extensive disease in the proximal segment cannot be completely eradicated.

Marked narrowing in the artery to be repaired may constitute a site for initiation of thrombosis; when such serious narrowing exists, replacement of the segment by a vein graft may be desirable.

Hemorrhage.—The use of heparin entails added risk from hemorrhage. Four of the patients in this series had sufficient bleeding from the wound while given heparin to alter their hospital course, and one patient died of hemorrhage. One other patient died of hemorrhage from a ruptured aneurysm formed at the distal end of the

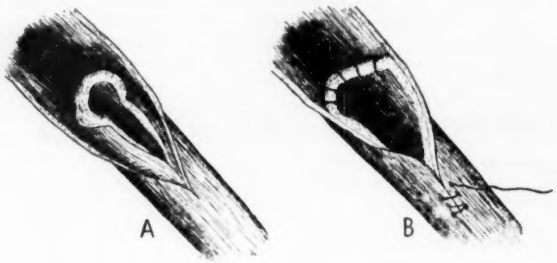

Fig. 1.—*A*, edge of intima at lower end of dissection. *B*, attachment of intimal flap to remaining medial wall by series of sutures.

repaired artery. The presence of a wound infection in this patient probably contributed to the formation of the aneurysm. Infection in the proximity of an arterial suture line is an ill omen, and all persons in attendance should be prepared to use effective measures to control sudden hemorrhage.

The prevention of formation of aneurysms due to inadequate resistance of the arterial wall with the use of fascia lata has been reported.[2a] Where the arterial wall appears too thin to support the arterial pressure, it may also be possible to substitute venous or arterial grafts.

Extensive Distal Arterial Obstruction.—The routine use of lower segment femoral and popliteal arteriograms at the time of operation to supplement the preoperative arteriograms should enable the surgeon to avoid ill-fated endarterectomy where hopeless disease exists beyond his scope of surgical attack.

There is an important group of patients in whom there is an obstruction of the femoral artery and in whom there is no refilling of the lower femoral segment on the preoperative arteriogram. By ordinary criteria these patients are unacceptable for surgery. In six patients with nonvisualized lower segments exploration has recently

been done at the level of the popliteal artery. In the first two an apparently satisfactory popliteal artery was found. No arteriogram was done, and endarterectomy was accomplished. Persistent pain at rest and failure to improve led to amputation which demonstrated severe distal arterial obstruction.

The third patient had a satisfactory popliteal artery, and endarterectomy was performed with a good result. The fourth and fifth patients appear to have satisfactory popliteal arteries, but arteriograms done at the time of operation revealed extensive obliterative vascular disease. Because of the presence of gangrene in the foot both patients underwent immediate amputation without endarterectomy. The popliteal artery of one of these patients is shown in Figure 2. At one end the initiation of the intimal dissection may be seen; a few centimeters distally at the other end of the segment there is almost complete obstruction of the lumen. The sixth patient who underwent such exploration was shown to have a good arterial lumen without obstruction in the distal vessels and has had an excellent result from his endarterectomy.

Diffuse Severe Arteriosclerosis.—The history of recent coronary occlusion or cerebrovascular accident, the presence of nephrosclerosis, or the demonstration of obliteration of multiple major arteries indicates the presence of such a severe disease

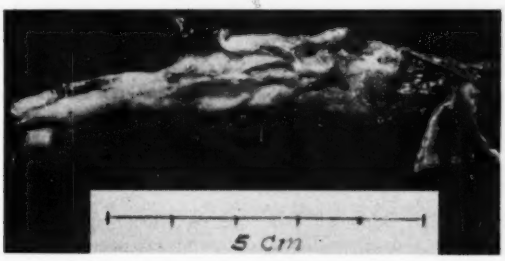

Fig. 2.—Obliterative vascular disease in popliteal artery from patient who underwent amputation. Note intimal flap being raised proximally at right, and extensive disease seen distally at left.

that extensive surgical attack upon a localized manifestation is unjustified. Two patients in this series fall into this class. One (J. A. W.) has since been incapacitated by hemiplegia. In another (W. H. F.) a renal and a superior mesenteric artery thrombosis developed during operation. The latter was successfully treated by removing the plaque at the orifice of the superior mesenteric artery, but the former caused his death five days later. Nine other patients were refused surgical treatment on the basis of severe arteriosclerosis.

SUMMARY AND CONCLUSIONS

The number of good results following endarterectomy may be expected to increase as the principles of selection of patients for this operation are clarified. The more localized the disease, the better the result may be expected to be.

Techniques have been recommended for avoiding the hazards of thrombosis in the endarterectomized segment and for avoiding the performance of endarterectomy on those patients whose extensive distal arterial disease precludes a satisfactory result.

The use of heparin is justified in spite of some added risk from hemorrhage. Formation of an aneurysm and rupture constitute another danger, which may be minimized by suggested techniques.

DISCUSSION

ON PAPERS BY DRS. OLWIN, DYE, AND JULIAN AND DRS. BARKER AND CANNON

DR. G. ARNOLD STEVENS, Beverly Hills, Calif.: Concerning the excellent presentation by Dr. Olwin, as far as I know it speaks for itself, and I have nothing to add.

I asked Dr. DeBakey to discuss the paper by Dr. Barker, but he was reluctant to do so on the basis that, as he stated, his experience was limited to a series of one case. After he hears me he may change his mind and decide to discuss it after all.

It is true that during the past year I have been interested in and concerned with the problem that Dr. Barker has reported to us today. If it is permissible for one to compliment one of his own group at the University of California School of Medicine at Los Angeles, I should like to commend Dr. Barker for his report.

As we all know, arteriosclerosis is a common disease. The number of patients so afflicted who have major arterial obstruction is relatively large. Despite this, little effort has been directed toward a direct attack upon this phase of the disease. Endarterectomy, as described by Dr. Barker, does constitute such an attack.

From a technical standpoint, from what I have seen, it does seem to me that suturing of the intima, as described by Dr. Barker, does minimize surgical postoperative thrombosis.

On the basis of available data, including that of Dr. Barker, it seems to me that three things are evident: First, endarterectomy, as described, is a formidable procedure. It is not devoid of major surgical complications. Furthermore, it is not uniformly attended by good results.

Second, for these reasons it also seems to me that widespread adoption of the procedure at this time is probably not justified.

Third, in a certain group of properly selected cases the operation seems to be here to stay. I think it is reasonable to assume that further experience in the selection of cases will enlarge the scope of its application.

DR. RICHARD PATTON JR., Columbus, Ohio: At the Ohio State Medical Center we are in agreement with Drs. Olwin and Julian that a late peripheral embolus can be removed successfully. The majority of late emboli, as we all know, are accompanied by a complete block of the circulation and a loss of the extremity; but occasionally we find one that has sufficient collateral circulation to maintain blood flow in the major artery below the embolus, and this allows us to do a late embolectomy with good results.

I should like to demonstrate the fact that we use aortography to delineate the area of block, to accurately localize it, and to bring out the presence of the circulation in the major artery below the block.

[Slide] This slide shows the block present in the superficial femoral artery on this side, this being the profunda femoral. I think you can see the obstruction on that side. This is the aortogram, the film taken just at the completion of injection of the dye into the aorta.

[Slide] This slide was taken three seconds later, and shows the block and also the circulation in the superficial femoral artery below the site of the block on each side. This patient had an embolus, diagnosed clinically by the fact that she had markedly damaged circulation. It was diagnosed by aortography as to localization and area of the block. She had successful removal of her embolus from the right side one week after its occurrence, and from the left side two weeks after the occurrence of the emboli.

It was felt that in this patient, because of the severe clinical symptoms of a decreased circulation, and an arterial block with evidence of circulation in the major artery below the block, operation and late embolectomy were feasible. It brought about clinical recovery of the patient as evidenced by normal pulsations and normal oscillometric readings postoperatively.

DR. JOHN H. OLWIN, Chicago: In closing, I should like to thank the discussers for their kind remarks, and I should like also to say just one word on Dr. Barker's paper.

The problem of endarterectomy has been a very confusing one to those who have had anything to do with it. What the limits are is one of the most difficult problems. We have combined intimectomy and thrombectomy with arterial replacement with a venous graft, an autograft wherever possible, and, in some instances, a homograft. In most instances when we do a resection of the vessel there is a certain amount of intimectomy that is necessary, particularly because resection of the vessel to normal intima as a rule means the destruction of certain collateral vessels. And this may leave the patient in a worse condition than before surgery. Therefore, it has been our rule that we will not resect a collateral vessel of any size, even though we may not be able to do a successful graft; but we do not hesitate to intimectomize beyond these collateral vessels.

The point that Dr. Barker made, of the flap of intima which may catch blood as it flows past the flap, is a very good one. In many of our cases we have had to leave such a flap. In the one successful bilateral graft which we have done for obstruction of both superficial femoral arteries—the longest graft we have made, incidentally, being 32 cm.—we have left this type of flap in both of those instances. So, I think in some instances in which there is a very small and thin flap it can be left without too great a risk, although I certainly agree that if one can resect to normal intima one should do so.

Also a word about the interpretation of arteriograms: When we do a graft and resection of the vessel, we like to see, in the arteriogram, an open vessel below the obstructed segment. However, in some of our successes we have not had this lower segment visible on arteriography. We have adopted the principle of exploring those vessels anyway, unless there is evidence of a gradual deterioration of the vessel distally so that we are reasonably sure it is not a segmental obstruction and is primarily a generalized atherosclerosis with obliteration of the peripheral vessels.

Dr. Wiley F. Barker, Los Angeles: I want to thank Dr. Stevens and Dr. Olwin for their kind remarks. I am delighted to find that the experience Dr. Olwin has had is very much parallel to ours.

I should like to make a rather brief closing comment in trying to clarify what I should consider the type of patient as the choice for endarterectomy.

In the first place, I believe rarely will patients over 60 be satisfactory, because in the group older than 60 there will be too many complicating forms of arteriosclerosis. Whether they are over 60 or not, they should have no significant arteriosclerotic disease or major basic pathology elsewhere.

A good distal artery should be demonstrable by either the preoperative arteriogram or by the arteriogram performed directly at the time of operation when the vessel is exposed.

May I say that by all means the shorter the extent of the block and the higher it is, the more satisfaction can be expected from the results?

RECONSTRUCTION OF BURN-SCAR DEFORMITY

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MODERN methods of treating severe burns have greatly reduced the incidence of serious scar deformities. With the advent of the antibiotics in the control of infection and the development of techniques for early and successful skin grafting, residual impairment should be less than in former years. Unfortunately, the early treatment is not always effective. Moreover, it is obvious that in deep burns which destroy anatomical structures, some degree of scar deformity is inevitable.

The degree of the cicatricial deformity is relative to the severity and location of the burn. By definition, first-degree burns involve only the epidermis and should heal without scarring. In second-degree burns, where there is partial destruction of the dermis, there is a variable amount of disfigurement due to superficial scar. This will depend upon the thickness of the skin and the area affected, as well as upon complications such as bacterial infection. Third-degree burns, in which the full thickness of the skin and varying amounts of the underlying tissues have been destroyed, will heal only by scar formation. With extensive loss of deep tissues, subsequent scar contracture will develop.

Burn-scar contractures result from a shortening of the soft tissues during the healing process. The adjacent soft parts and often the underlying skeletal structures are drawn into abnormal position. When this occurs, appearance, as well as function, is impaired. The presence of poorly nourished scar epithelium will, in many cases, cause ulceration and further complications. The nature of the scar deformity will depend primarily on the depth of the destruction and on the location and extent of the burn. The healing characteristics of the patient further influence the type of scar formation.

Numerous categories have been proposed to include the different kinds of burn scars. The simplest classification lists flat, depressed, or contracted scars, hypertrophic scars, and true keloids, with various degrees of each. Further breakdown of the different types includes unstable, poorly healed, and chronic ulcerated scars

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which may become malignant. A comprehensive and detailed study of the etiologic factors and the pathology of keloids and hypertrophic scars has been presented by Trusler and Bauer [1] and recently by Mowlem.[2] Using an experimental approach, Min-Chyang Ju [3] has attempted to explain the mechanics of scar contraction and has correlated the clinical phenomena on a physical basis. He also studied the results obtained in the repair of various types of constricting deformities in which the direction of scar pull had been changed. Further studies on the pathology and behavior of scar tissue, as well as on the basic principles of wound healing, will prove increasingly valuable. These will greatly aid in the understanding of the proper surgical approach to reconstruction of such deformities.

With the aftermath of two World Wars, surgeons have had to overcome the therapeutic problem involving mass reconstruction of soft tissue traumata. The use of simplified techniques and improved supportive therapy has produced superior results. The current tendency is to avoid extensive multiple-stage procedures, employing free-skin transplants and the transfer of local tissues whenever possible.

OPTIMUM TIME FOR SURGICAL CORRECTION

Theoretically, the optimum time to begin reconstructive surgery is when the scar tissue is mature but before serious contractures have developed. This may vary from six months to a year after initial healing. At this time, scar tissue tends to be softened and relaxed. An extended waiting period may be justified when the scar deformity continues to show signs of improvement. In some cases surgical correction may not be necessary.

When surgery is indicated, there may be factors which prevent intervention at the proper time. Sometimes the surgeon does not meet the reconstructive problem until several years have elapsed since the initial injury. When extensive reparative work is indicated, it may be necessary to spread the surgical program over a period of time in order to maintain the good health of the patient. With children particularly, the repair work should parallel the growth curve. Areas where anatomical development may be retarded or deformed are given primary consideration. This factor should determine the chronological order of surgical procedures. The number of reparative measures required and the healing power of the patient will further influence the elected time for surgery.

BASIC TYPES OF DEFORMITIES AND PLANS FOR RECONSTRUCTION

Among the commonest and disabling burn-scar deformities are those involving areas of motion. These include the regions about the eyelids, mouth, and neck, and between the trunk and extremities. Likewise, the extremities at any or all flexor surfaces may develop contractures with severe functional impairment. Areas about the face, neck, and hands also produce serious problems from the standpoint of appearance as well as function. Disfiguring burn scars of these regions may be of particular concern to the patient because of the accompanying psychological stigma.

1. Trusler, H. M., and Bauer, T. B.: Keloids and Hypertrophic Scars, Arch. Surg. **57**:539, 1948.

2. Mowlem, R.: Hypertrophic Scars, Brit. J. Plast. Surg. **4**:113, 1951.

3. Ju, D. M. C.: The Physical Basis of Scar Contraction, Plast. & Reconstruct. Surg. **7**:343, 1951.

An over-all planned program for reconstruction of existing deformities is imperative. Ill-conceived and hastily executed procedures will usually be fraught with disappointment. In cases involving multiple procedures, the plan should indicate the problems to be corrected first. As previously mentioned, the correction of contractures which retard growth is of primary importance. For example, the female child with a burn scar involving the anterior chest wall will need scar revision as breast development occurs. Long-time planning will aid in meeting these problems which are not evident in the early stages of cicatricial deformities. In this connection, the preservation of valuable donor sites for later skin-grafting procedures is often advisable.

The plan for reconstruction of a specific deformity narrows down to the selection of the technique to be used. There is no one standard procedure that can always be prescribed for any one type of deformity. The choice is based on many factors. Consideration must be given to the amount and type of scar to be replaced, as well as to the individual healing characteristics of the patient. The location of the deformity with the associated problem of functional restoration will further influence the selection of procedure. Functional impairment may often dictate the use of pedicle flaps to restore subcutaneous tissue and epithelial coverage. This applies particularly to regions where tendon transplants are contemplated. Likewise, pedicle flaps to weight-bearing surfaces will best accommodate functional replacement. Other relevant considerations in choosing a technique should include color match and texture of skin transplants, as well as availability of suitable donor sites.

Complete excision of scar tissue is advisable whenever possible. Then the wound may be closed with adjacent normal tissue or with the application of a split- or full-thickness skin graft to the defect. In severer deformities which require reconstruction of contour as well as surface defects, the transposing of local or distant pedicle flaps may be indicated. Where existing tissue is adequate, as in binding webs, the Z-plastic operation is the method of choice. The Z-maneuver is also used in combination with other methods to give improved results.

Finally, any reconstructive plan which involves lengthy and costly hospitalization must be justified by the improvement obtained. Time-consuming procedures should be supplanted, whenever feasible, by the simpler methods of free grafting or local flap transposition. Various types of corrective measures and specific indications for their use will now be considered.

SPLIT-SKIN GRAFTS

Split-skin grafts of various degrees of thickness constitute the simplest method of repairing large superficial scar defects. These grafts gave satisfactory results as to appearance, stability, and "take." The introduction of the various dermatome instruments has permitted a more universal use of sheet grafts in massive coverage of soft tissue defects. Freehand grafts are still employed successfully, but dermatome grafts are more consistent in thickness, size, and shape. These grafts can also be patterned to the exact dimensions of the defect. This advantage is enhanced by the use of nylon backing, as described by Glanz and Trusler [4] in another paper.

4. Glanz, S., and Trusler, H. M.: The Application and Use of Nylon-Backing with Split-Skin Grafts, Plast. & Reconstruct. Surg. **8**:94, 1951.

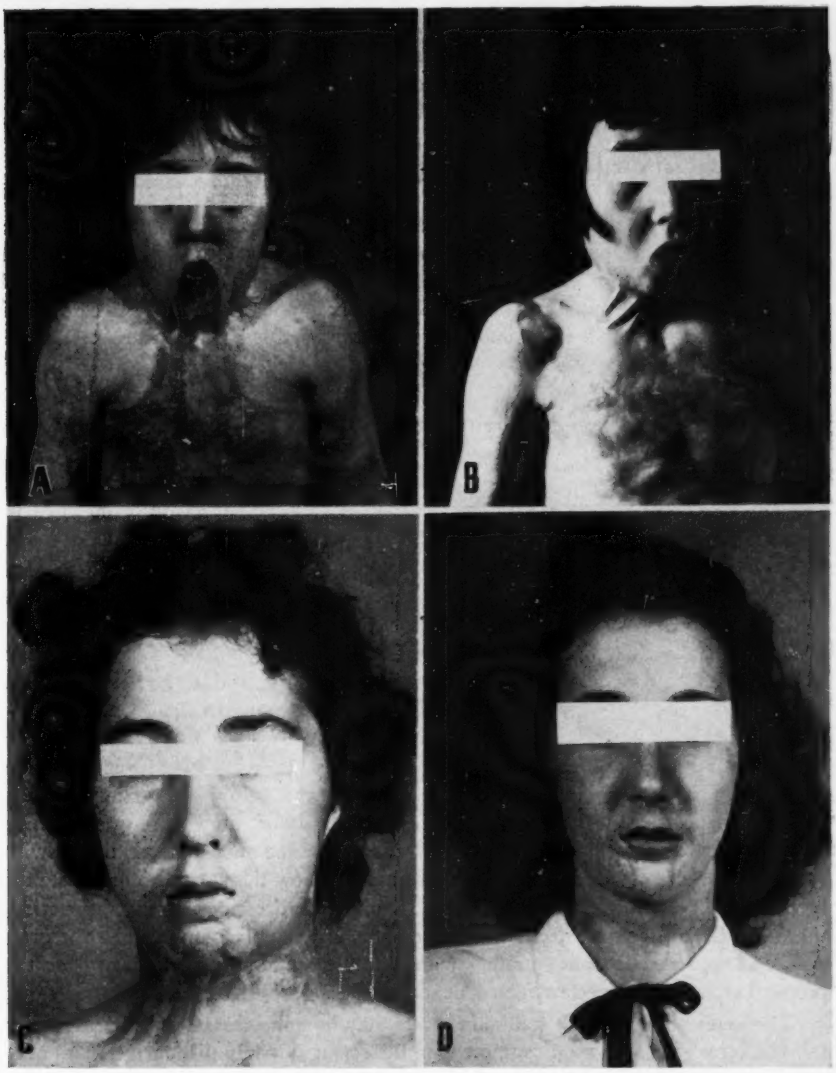

Fig. 1.—*A*, extensive scar contracture of face and neck, resulting from spontaneous healing of severe burns. *B*, two years later with partial release of contracture and application of split-skin graft. *C*, appearance 11 years later after further excision of scars and additional grafting. *D*, fifteen years following initial repair. Neck and face deformities have now been corrected by multiple-stage split-skin grafting. Mouth and chin have been restored to normal contour by release of scar contracture.

Many disfiguring neck deformities can be corrected with the use of intermediate split-skin grafts (Fig. 1). Adjacent, as well as distant, pedicle flaps have also been advocated as the proper technique for the repair of neck contractures. Reasons given include the off-color appearance of a free graft and the tendency to subsequent shrinkage and wrinkling. We have not found these factors so prevalent as to counteract the advantages and comparative simplicity of a free-skin transplant. When all the scar tissue has been excised and the proper graft thickness has been used, results are generally satisfactory. The utmost care must be observed, however, in the application of a proper dressing and immobilization of the graft to assure complete take. Whenever possible, comparable matching donor sites should be selected. We have found the submammary region of the anterior chest wall to compare somewhat in texture to the skin of the neck. In females, the factor of color match can be well camouflaged with the application of cosmetics. The problem of color, however, is of much greater significance in regions about the face. Shaded color differences on the neck are not too obvious.

In burn scars about the chest region, split-skin grafts frequently serve a useful purpose. The scar pull can be relieved by simple incision and intermediate-thickness grafts applied to the defect. This is especially effective in the relief of female breast contractures. The release of constricting scar lines will allow the return of normal anatomical configuration. The restoration of contour can thus be accomplished in one procedure. Any depression of the grafted area is usually overcome with the deposition of subcutaneous fat within three to six months.

Another use of split-skin grafts of intermediate thickness is in the correction of contractures on the flexor surfaces of the extremities. These are most commonly found in the antecubital and popliteal spaces. The paramount factor in restoration of normal function is the prevention of a vertical-line scar across the flexion crease. The initial incisions should be designed in an oblique or horizontal fashion. Complete dissection of all scar tissue is of utmost importance. Usually after this has been done, the extremity can be returned to its full extension with no evident limitation of motion. If the joint structure is involved, however, complete functional return may not be possible. After the excision of all scar tissue, immediate grafting may not be advisable. Owing to the irregular contour of the subcutaneous tissue, with possible exposure of tendon or muscle, it is best to allow the wound to granulate for several days prior to grafting. With the use of sterile dressings during this period, there is little chance for infection or other untoward complications. When the graft has been applied, adequate splinting with absolute immobility is necessary for the proper healing of the reconstructed flexor surface.

The application of thick split-skin grafts may in some cases supplant the use of full-thickness grafts. A good example is in the repair of badly disfiguring scars over the dorsum of the hand (Fig. 2). A thick split-skin graft properly applied will not shrink or wrinkle and will resemble the skin of the dorsum in texture and pliability. To meet these qualifications the best donor site is the lateral aspect of the thigh. A thick graft may thus equal the advantages of a full-thickness transplant and, moreover, allows spontaneous healing of the donor site. This technique has been described by Greeley.[5]

5. Greeley, P. W.: Plastic Repair of Extensor Hand Contractures Following Healed Deep Second Degree Burns, Surgery **15**:173, 1944.

The use of split-skin grafts of thin calibration should be limited to coverage of granulating wounds in the initial treatment of thermal injuries. There is more assurance of donor site healing and greater probability of complete take. However, thin split grafts are prone to wrinkling and shrinkage, and for this reason are not advisable in the secondary repair of cicatricial deformities.

The selection of a donor site is significant in any skin-grafting procedure. An unwise choice may produce further disfiguring visible scars. The use of a dermatome may facilitate more careful selection of concealed donor areas. Moreover, these sites heal more consistently with a lessened risk of residual scarring when grafts are taken at the proper depth. It must be stressed, however, that donor sites can be ruined for future use by improper cutting of skin grafts, using either freehand or dermatome techniques. This includes grafts that are cut too deep through the

Fig. 2.—*A*, keloid and burn scar contracture of hand and forearm. *B*, two years after repair, with scar excised and areas resurfaced by thick split-skin grafts.

full thickness of the skin, resulting in donor areas which are difficult to heal. The conservation of donor sites for possible reuse is of prime importance when multiple procedures are necessary.

FULL-THICKNESS GRAFTS

Full-thickness skin transplants, when properly selected, have the advantage of improved texture. In comparison with split grafts, they are less likely to contract and wrinkle. It is generally agreed that full-thickness grafts should not be used on primary granulating wounds. Their disadvantages are a frequent poor take over large areas, as well as the destruction of donor sites for future use.

In a recent collective review, Greeley [6] has described the indications for the use of full-thickness skin grafts. Emphasizing their limitations in the correction of

6. Greeley, P. W.: The Full-Thickness Skin Graft: Collective Review, Plast. & Reconstruct. Surg. **9**:64, 1952.

larger deformities, he pointed out the danger of an incomplete take. Complications following poor take will counteract the cosmetic and functional advantages of a full-thickness graft. Greeley outlined certain fundamental principles to be observed in assuring successful use of these grafts. They included absolute asepsis, a dry field, an accurately cut graft, and proper pressure and immobilization in a dressing.

The full-thickness skin graft finds its greatest value in the reconstruction of relatively small defects of the face and hand. In severe ectropion of the eyelids, these grafts are ideal replacement tissue after the cicatricial contracture has been excised (Fig. 3). Likewise, defects about the lips and nasolabial folds can be similarly repaired. The recurrence of secondary contracture in these mobile areas is offset by the depth and pliability of these transplants.

Fig. 3.—*A*, unhealed scar of forehead three months following burn. Ectropion of upper eyelid due to burn-scar contracture. *B*, defects corrected by excision of ulcerated forehead scar and application of split-skin graft with simultaneous correction of ectropion by postauricular full-thickness graft to eyelid. Eyelids were sutured together for approximately three months following surgery to prevent recurrence of ectropion.

In surface deformities of the hand, we restrict the use of full-thickness grafts to the fingers and palmar surface. These grafts meet the requirements of flexibility and durability desired in this area. Burn-scar contractures of the fingers will respond well to tissue replacement by an adjacent flap in combination with a full-thickness graft. In the application of the graft, however, vertical lines across the flexion creases must be prevented. Suturing should be planned to form transverse or oblique scar lines over any of the joint creases. If this basic tenet is violated, subsequent healing will be fraught with disappointment. Secondary scar contracture following a faulty repair may result in a similar or severer deformity.

Tactile sensitivity and discrimination in full-thickness grafts to the hand have been found to be uniform despite the use of different donor sites. Hutchinson and his associates [7] have examined the regeneration of sensation in grafted skin. They

7. Hutchinson, J.; Tough, J. S., and Wyburn, G. M.: Regeneration of Sensation in Grafted Skin, Brit. J. Plast. Surg. **2**:82, 1949.

concluded that under optimum conditions full-thickness skin grafts tend to assume the sensory pattern of the skin of the region to which they have been grafted.

Brown and his colleagues [8] have advocated the use of full-thickness grafts in the repair of cicatricial deformities of the neck. The texture and color match may be superior to split-skin grafts, but the possibility of incomplete take over such a large area cannot be minimized. As explained previously, we prefer the use of intermediate split-skin grafts in the repair of neck contractures.

The selection of a donor site will contribute to the success or failure of a full-thickness graft. Postauricular grafts compare favorably in color, texture, and thickness with the skin of the face. They are most successfully used in correcting contractures about the eyelids, nose, lips, or other small defects. Moderate size grafts from the postauricular region can be easily obtained with primary closure of the wound. If a greater amount is necessary, the donor defect can be covered with a split-skin graft. Supraclavicular skin offers an alternative source for complete-thickness grafts. However, the donor site may be visibly scarred. Full-thickness grafts used for the hand may be taken from the abdominal or superior inguinal regions, cautiously avoiding hair-bearing areas. The color match is often poor, but the thickness and texture are ideal for the palmar surface of the hand. Occasionally, postauricular grafts may be used for more effective color match. Frackleton [9] has further suggested the use of antecubital skin for full-thickness grafts of the hand.

LOCAL AND DISTANT PEDICLE FLAPS

The pedunculated flap transfers a solid mass of skin, subcutaneous fat, and fibrous tissue from one area of the body to another. In the repair of many deep deformities, this has a decided advantage over split- and full-thickness skin grafts, which do not include any of the subcutaneous tissues. Local or distant pedicle flaps thus may be indicated when an area is densely scarred, poorly vascularized, or void of subcutaneous fat and fibrous tissues. This applies principally to contractures involving bony prominences or large areas of motion. It is obvious that a pedunculated flap should be used whenever the defect involves the oral or nasal cavity or in any other situation where a large fistulous communication exists. In this instance the flap utilized must be supplied with a skin-graft lining (Fig. 5).

Local flaps may be designed to have permanent blood-carrying pedicles that are never severed at the base. Brown and his associates [10] have recently recommended a more frequent use of this type of flap and have outlined its indications. In contrast with all other transplants, the local flap actually supplies blood to the recipient area instead of depending upon the new site for nourishment. The distant flap, upon severance of its pedicle, must depend on local tissue vascularity. Another advantage of the local flap over the distant pedicle is the decreased time element involved. Fewer and simpler procedures are required. Whenever possible, therefore, the use

8. Brown, J. B., and McDowell, F.: Skin Grafting, Ed. 2, Philadelphia, J. B. Lippincott Company, 1949.

9. Frackelton, W. H.: Personal communication to the authors.

10. Brown, J. B.; Fryer, M. P., and McDowell, F.: Permanent Pedicle Blood-Carrying Flaps for Repairing Defects in Avascular Areas, Ann. Surg. **134**:486, 1951.

of a local pedicle flap should be given preference over a distant-flap procedure. Varying types of local flaps have been described by Aufricht,[11] Kazanjian,[12] Brown,[13] Mills,[14] and Conway.[15]

Rotation of contiguous flaps is effectively utilized in the repair of facial deformities. Ferris Smith[16] has long advocated their use and has reported consistent success in an extensive series of completed cases. Local rotation of flaps will accomplish restoration of normal facial contour without sacrificing the color or texture of the skin appearance. Frequently in this type of procedure scar tissue can be excised and a facial flap rotated in a one-stage operation. In the repair of small defects, the elasticity of facial skin will allow primary closure after the flap rotation. Incisions can be concealed within the hairline or along the natural creases of the face. When a postauricular flap is brought forward, a split-skin graft may be used to cover the residual donor defect.

The use of a forehead flap will also necessitate replacement by a free-skin transplant. Flaps brought down from this region will effectively fill defects around the orbital and nasal areas. In a man with a heavy beard, transverse scalp flaps may be rotated downward to replace an extensive defect of the middle third of the face.[17] Neck-rotation flaps play an important role in the repair of deformities of the lower third of the face. The advancement of a flap from the submandibular region will allow semiconcealed skin grafting of the donor site.

The success of rotation flaps in the region of the neck and face depends upon the presence of adjacent unscarred donor areas. The tissue of the flap must have normal elasticity and a good blood supply in order to assure viability. Whenever possible, the use of contiguous tissue in reparative procedures about the face is superior to other suggested methods.

Local flaps have widespread use in conjunction with free-skin grafts in almost any area of the body. The shifting of normal tissue to a region of excised scar with a graft to the donor site may prove more successful than a direct skin transplant to the scarred area. The blood-carrying pedicle will take better over the scar bed than a free graft and will result in improved appearance as well as function. It should be stressed, however, that the use of large pedicle flaps usually requires one or more delay operations. Large local flaps which are improperly planned and hastily executed often fail to survive.

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11. Aufricht, G.: Evaluation of Pedicle Flaps Versus Skin Grafts in Reconstruction of Surface Defects and Scar Contractures of the Chin, Cheeks, and Neck, Surgery **15**:75, 1944.

12. Kazanjian, V. H.: Treatment of Deformity from Burns, Connecticut M. J. **8**:661, 1944.

13. Brown, J. B.; Cannon, B., and McDowell, A.: Direct Flap Repairs of Defects of Arm and Hand: Preparation of Gunshot Wounds for Repair of Nerves, Bones and Tendons, Ann. Surg. **122**:706, 1945.

14. Mills, J. T., and Patterson, J. B.: The Combined Use of Multiple Excision, the Z-Plastic and Sliding Flaps in the Correction of Certain Congenital and Acquired Anomalies, Plast. & Reconstruct. Surg. **2**:249, 1947.

15. Conway, H.; Stark, R. B., and Kavanaugh, J. D.: Variations of the Temporal Flap, Plast. & Reconstruct. Surg. **9**:410, 1952.

16. Smith, F.: Flaps Utilized in Facial and Cervical Reconstruction: Collective Review, Plast. & Reconstruct. Surg. **7**:415, 1951.

17. Barsky, A. J.: Use of One Flap to Restore Extensive Losses of the Middle Third of the Face, Ann. Surg. **118**:988, 1943.

In circumstances involving extensive avascular regions with severe loss of subcutaneous tissues, and in which bone replacement is anticipated, distant pedicle flaps are indicated. Gillies [18] was the first to advocate extensive use of tube pedicles in major facial reparative procedures. He has been followed by many others, including Pierce,[19] Ivy,[20] Macomber,[21] Cannon,[22] Barsky,[23] and McNichol.[24] Tube grafts are valuable in the repair of facial deformities when normal contour has been destroyed and local tissue is not available (Figs. 4 and 5). These flaps will require a skin-graft lining for the reconstruction of nasal and oral cavities. Pedicles advanced from distant areas may be employed in the reconstruction of burned ears as well as in major nasal and facial defects. Cartilage implants are more easily inserted in this type of flap in subsequent reparative procedures.

Weight-bearing surface defects about the extremities are best covered by pedicle flaps which include skin and the subcutaneous layers of fat and fibrous tissues. Cross-leg flaps are a good example of this type of repair. Stark [25] has covered the subject well in a recent review. He also investigated the problem of vascular mechanics in relation to cross-leg flaps, which is applicable to the use of other forms of distant pedicles. The distribution of arterial and venous blood supply in the course of the pedicle will determine the success of transplantation. It is generally assumed that delay procedures automatically increase the blood supply of the pedicle. This, however, may not be the case. It should be emphasized that an intermediate stage may cause thrombosis of the essential blood supply and result in irreparable damage to the flap. In specific instances direct transfer of pedicle flaps can be successfully accomplished. A good example is a broad-based short-pattern flap from the abdomen to the arm, as described by Blocker.[26]

Flaps brought from distant areas, however, usually involve multiple procedures. For this reason, the patient's attitude as well as the time and expense involved should be considered before such reconstruction is initiated. The expected improvement must warrant the selected procedure. The entire problem of the most effective use of both local and distant pedicle flaps about the head and neck has been covered in a comprehensive monograph by New and Erich.[27]

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18. Gillies, H. D.: Plastic Surgery of the Face Based on Selected Cases of War Injuries of the Face, Including Burns, London, Oxford University Press, 1920.

19. Pierce, G. W.: Reconstruction of the External Ear, Surg., Gynec. & Obst. **50**:601, 1930.

20. Ivy, R. H.: Repair of Facial Defects with Low-Neck Pedicle Flaps, Plast. & Reconstruct. Surg. **1**:119, 1946.

21. Macomber, W. B., and Berkeley, W. T.: Use of Neck Tubed Pedicles in Reconstruction of Defects of the Face, Plast. & Reconstruct. Surg. **2**:585, 1947.

22. Cannon, B.; Lischer, C. E., and Brown, J. B.: Open Jump Flap Repairs of the Lower Extremity, Surgery **22**:335, 1947.

23. Barsky, A. J.: Principles and Practice of Plastic Surgery, Baltimore, Williams & Wilkins Company, 1950.

24. McNichol, J. W.: Total Helix Reconstruction with Tubed Pedicles Following Loss by Burns, Plast. & Reconstruct. Surg. **6**:373, 1950.

25. Stark, R. B.: The Cross-Leg Flap Procedure, Plast. & Reconstruct. Surg. **9**:173, 1952.

26. Blocker, T. G., Jr., and Mithoefer, J.: The Pattern Flap, Plast. & Reconstruct. Surg. **5**:163, 1950.

27. New, G. B., and Erich, J. B.: The Use of Pedicle Flaps of Skin in Plastic Surgery of the Head and Neck, Springfield, Ill., Charles C Thomas, 1950.

Fig. 4.—*A*, unhealed scar of face and neck six months following third-degree burns. Note ectropion of lower eyelid and lip caused by scar contracture. *B*, intermediate stage of repair with tube pedicle brought up from lateral chest wall. Roll flap is now in position for severance of pedicle in axilla. Tube will be unrolled for application to side of face. *C*, result one year later after utilization of pedicle to correct face and neck contractures. Note complete functional restoration of eyelid and lower lip. *D*, appearance of patient 13 years later after scar revision. It should be noted that in this case a satisfactory result might have been obtained by split-skin grafting without recourse to the more protracted tube pedicle procedure.

Fig. 5.—*A*, complete loss of soft tissue through side of face due to contact burn while asphyxiated. In this deformity repair could be accomplished only by a thick flap of tissue with an epithelial lining. *B*, pedunculated tube flap advanced from chest wall. Prior to transfer, flap was lined with a full-thickness skin graft to give an inner surface to the cheek. *C*, intermediate stage showing tube flap in position to be completely unrolled into the defect. *D*, result two years after initial injury, with major reconstruction completed. Scar revision could further improve appearance if patient desired.

Z-PLASTIC PROCEDURES

The Z-plastic operation embraces the principle of local transposition of triangular flaps of skin to release abnormal scar contractures. The many advantages of this procedure have been described by Koch,[28] Davis,[29] Mills,[14] Stevenson,[30] Sutton,[31] Smith,[32] and others. The Z-technique finds its best application in those instances in which the surrounding skin is of essentially normal texture and in which a web of scar contracture exists. The presence of pliable tissue on each side of the web is an important factor. In these circumstances the effective release of contracted scars, webs, or bands can be accomplished utilizing local tissue in a Z-plastic maneuver.

In scar contractures resulting from severe burns, the area may be partially or completely infiltrated with fibrous tissue. Excision of these contracting bands can often be followed by a simple transposition of triangular flaps. When local tissue is adequate, the Z-procedure alone will relieve the deforming contracture and restore normal contour and function. If there is an inadequate amount of adjacent normal skin, scar tissue may be utilized. We do not advocate this. It is better to discard scar tissue of questionable viability and to cover the defect with a free transplant in conjunction with the Z-procedure. This also permits correction of the defect in one operation. Frequent, extensive contracting scars will not respond to a single Z-maneuver. The procedure may then be extended with multiple Z-incisions forming a series of interdigitated flaps.

Scar deformities in selected areas about the face are especially amenable to Z-plastic correction. Moderate contractures of the eyelids and nasolabial folds can be effectively released with a simple or multiple Z-procedure. This also applies to purse-string deformities of the oral stoma. Occasionally, it may be necessary to add a free graft if the Z-plastic does not offer complete coverage of the raw area. For this purpose, full-thickness skin grafts, matching in color and texture, give the best results.

Deep contracting scars about the neck and axilla respond well to correction by single or multiple Z-incisions (Fig. 6). An intermediate-thickness split graft may be used here to cover any remaining raw surface. In the reconstruction of axillary web contractures, the excess scar epithelium may in some instances be utilized without recourse to a free transplant of skin. Cicatricial webs in the well-known bat-wing deformity develop satisfactory circulation. If the triangular incisions are not too large, successful relaxation can be obtained by using a minimal amount of scar tissue along with the adjacent normal skin (Fig. 7).

The Z-plastic procedure is also valuable in the correction of contractures involving flexor surfaces of the extremities. This applies particularly to the antecubital

28. Koch, S. L.: Burn Contractures of the Axilla, S. Clin. North America **14**:751, 1934.

29. Davis, J. S.: Present Evaluation of the Merits of the Z-Plastic Operation, Plast. & Reconstruct. Surg. **1**:26, 1946.

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31. Sutton, L. E.: Reconstruction of the Contracted Axilla, Plast. & Reconstruct. Surg. **1**:43, 1946.

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and popliteal spaces, the inguinal region, and the hands. Severe burn contractures in the flexor areas are repaired with continuous Z-shaped incisions which will release the constricting bands and alter the direction of the scar.

Fig. 6.—*A*, vertical scar contracture of lateral region of neck with limitation of motion and distortion of contour. *B*, one week following surgery, showing release of scar pull and restoration of contour by Z-plasty. *C*, appearance one year later with contour and motion of neck restored.

Fig. 7.—*A*, axillary web contractures resulting from spontaneous healing of severe burns. *B*, complete reconstruction of axilla in single operation by multiple Z-plasties. Split-skin graft was used to supplement available tissue in accomplishing Z-plasty repair.

Necrosis of any transposed tissue can be averted by cutting thick, wide, and short flaps. Cautious handling and suturing without tension will also aid satisfactory wound healing. If viability is maintained, the transposed flaps, including a minimal amount of scar tissue, will eventually stretch and become pliable. The care-

ful observation of these basic principles in the definitive repair procedure will result in prevention of the development of secondary contractures.

In summary, utilization of the Z-incision may obviate the necessity for extensive skin grafting or the delayed transfer of pedunculated flaps and tubes. Moreover, the Z-procedure may be used in conjunction with other reparative techniques. Properly outlined Z-incisions will prevent unsightly puckering at the junction of scar tissue and free grafted skin. The Z-plastic operation is effective in a number of situations when adequate local tissue is available. The universal value of the technique, however, can be overstressed. The advantages may be lost when attempted utilization of adjacent tissue is carried beyond its normal limitations.

ADJUNCTS TO THE CONTROL OF SECONDARY SCAR FORMATION

After the repair of the original cicatricial deformity, the utmost care should be exercised to prevent formation of secondary contractures. If this part of the procedure is neglected, a good result may be vitiated by the development of subsequent scar hypertrophy. For the majority of cases, prophylactic measures against secondary scar formation consist of the local application of pressure dressings and lubricants. Where the tendency to form hypertrophic scars and keloids exists, radiation therapy is indicated.

Early compression dressings around the extremities, particularly in the lower limbs, will aid in the restoration of proper venous circulation. This can be accomplished by the use of elastic bandages. Of equal importance is the value of moderate pressure dressings over any residual scar to prevent overgrowth of fibrous tissue. For many years, we have treated scars about the face postoperatively with the application of small strips of adhesive tape until blanching of the recently healed scar occurs. Lubricants applied to a residual scar for as long as one year will further maintain pliability of the repaired tissue and prevent a drying or desquamation of a skin graft. Patients are warned, however, not to traumatize recently healed grafts by excessive massage.

If the patient has an active hypertrophic scar or keloid, it may be well to employ radiation therapy prior to surgical correction. After surgery, therapy should be reinstituted after the sutures have been removed. As stated in a previous publication,[1] we prefer the method of divided dosage. It should be emphasized, however, that continued and indiscriminate use of radiation therapy will prove more harmful than beneficial to the patient. The possibility of radiation damage has caused some surgeons to forbid the use of x-ray for this purpose. We have found, however, that when properly used, radiation therapy is of great benefit in the control of keloids and hypertrophic scars.

Functional rehabilitation after surgical correction is important in completing any program of reconstruction. Physical and occupational therapy can produce immeasurable improvement in the surgical result. When it is evident that the wounds are completely healed, passive and active motion are effective in restoring normal function. This should be stressed in areas where joints have been immobilized by contractures, with particular reference to the hand. Hydrotherapy is valuable in encouraging active motion. At the time of hospital discharge, patients are always instructed in the continued use of both physical and occupational therapy. They are then followed closely to assure continuation of good results.

SUMMARY

Early reconstruction of all burn-scar contractures is imperative if complications involving underlying muscular and bony structures are to be averted. Unnecessary postponement of reconstruction may often increase functional impairment as well as disfigurement. This applies particularly to growing children in whom atrophy of underlying tissues will cause irreversible damage to important structures.

A deformity resulting from a contracture usually will not improve with time. Surgical intervention is then the only recourse in restoring maximum function. The restoration of an acceptable appearance is of equal psychological importance. Consciousness of abnormal appearance will often induce morbid sensitivity and compensating defense mechanisms. These will seriously interfere with the patient's adaptation to normal living. Correction of the appearance therefore, as well as the function of a deformed part, is advisable to complete the rehabilitation of the patient to a useful happy life.

In the reconstruction of burn-scar deformities we have discussed four fundamental procedures as follows: split-skin grafts of varying thicknesses; full-thickness skin grafts; pedunculated flaps, local and distant, and Z-plastic techniques. In addition to these four basic procedures, it may sometimes be advisable to effect further improvement by simple excision and revision of unsightly scar lines.

Recent advances in modern plastic and reconstructive surgery enable the correction of burn-scar contractures in a decreased period of time. Improved skill and techniques coupled with a better control of wound healing have contributed to a more successful restoration of the disabled patient. Every person suffering from the crippling effects of burn-scar contractures can be helped to some extent.

ANOMALIES OF THE POSTERIOR TIBIAL TENDON

A Cause of Persistent Pain About the Ankle

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OBSERVATIONS of four cases of posterior tibial tenosynovitis in which anomalies of the tendon were found at surgical exploration has prompted a review of this subject. The syndrome of noninfectious tenosynovitis was first described by Velpeau, in 1818, and again in 1825.[1] The work of de Quervain,[2] in 1895, and of many others since has served to emphasize the importance of this condition as a cause of painful symptoms, particularly about the wrist and ankle.

Kulowski,[3] in 1936, was the first to mention tenosynovitis of the sheath of the posterior tibial tendon. This was also noted by Lipscomb,[4] who stated that it occurred in about 16% of cases of tenosynovitis and peritendinitis of the feet and ankles. Lapidus and Seidenstein[5] reported three cases of tenosynovitis with effusion involving the sheath of the posterior tibial tendon. Lipscomb noted anatomic variations of the tendons within the posterior tibial compartment.

INCIDENCE

Tenosynovitis of the posterior tibial tendon was diagnosed in 21 cases at the Mayo Clinic from 1935 to 1951, inclusive. Most cases were encountered during the past decade. The average age of the patients was slightly more than 40 years; 12 females and 9 males were affected. The left foot was involved in 12 cases and the right foot in 9. In two cases symptoms had been present in both ankles, although at the time of examination only one ankle showed signs of active disease.

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Fellow in Orthopedic Surgery, Mayo Foundation (Dr. Spear).

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 5, 1952.

1. Velpeau, A., cited by Thompson, A. R.; Plewes, L. W., and Shaw, E. G.: Peritendinitis Crepitans and Simple Tenosynovitis: A Clinical Study of 544 Cases in Industry, Brit. J. Indust. Med. **8**:150-160, 1951.

2. de Quervain, F.: Über eine Form von chronischen Tendovaginitis, Cor.-Bl. schweiz. Aerzte **25**:389-394, 1895.

3. Kulowski, J.: Tendovaginitis (Tenosynovitis): General Discussion and Report of One Case Involving the Posterior Tibial Tendon, J. Missouri M. A. **33**:135-137, 1936.

4. Lipscomb, P. R.: Nonsuppurative Tenosynovitis and Paratendinitis, Instructional Course Lectures, Am. Acad. Orthop. Surg. **7**:254-261, 1950.

5. Lapidus, P. W., and Seidenstein, H.: Chronic Non-Specific Tenosynovitis with Effusion About Ankle: Report of 3 Cases, J. Bone & Joint Surg. **32-A**:175-179, 1950.

SYMPTOMS AND SIGNS

The condition was of spontaneous onset in 15 cases. In five cases symptoms appeared after a twisting injury of the ankle and in one case a fracture of the ankle had occurred six years prior to the onset of symptoms. Symptoms had been present for less than six months in 13 cases, whereas in 6 cases they had been present for more than one year. The shortest duration of symptoms was two days and the longest was seven years. The feet were pronated in 11 cases.

The patients complained of pain and swelling about the inner aspect of the ankle and the inner malleolus. This pain was increased when the patient walked over rough ground and went up or down stairs. The pain occasionally extended up the medial side of the leg. The symptoms were usually relieved by rest and elevation of the leg.

Examination disclosed fullness along the posterior surface of the medial malleolus; at times the medial malleolus itself was involved in the swelling. Tenderness on pressure was present over the medial malleolus and along the sheath of the posterior tibial tendon. This tenderness was most pronounced just behind the medial malleolus and extended up toward the calf and at times distally to the navicular bone. Eversion of the foot and extreme dorsiflexion usually caused pain. Crepitus was noted occasionally.

Results of various laboratory tests, including the sedimentation rate of erythrocytes, were normal in all but three cases; in these the sedimentation rates were slightly increased to values of 30, 33, and 28 mm. in the first hour (Westergren method).

ANATOMIC VARIATIONS WITHIN THE POSTERIOR TIBIAL COMPARTMENT

Anomalies of tendons in the posterior tibial compartment are uncommon. Standard textbooks of anatomy usually fail to note these variations. Quain,[6] in his textbook, stated that variations of the posterior tibial tendon were first described by Le Double, who recognized the presence of two tendons within this sheath.

The posterior tibial muscle normally arises from the posterior and contingent surfaces of the middle and upper parts of the tibia and fibula. The posterior tibial tendon arises from the medial border of this muscle and passes down the leg beneath the tendon of the flexor digitorum longus to pass behind the medial malleolus in the medial compartment on the medial collateral ligament; it passes deep into the flexor retinaculum and reaches its insertion into the navicular bone. It also inserts by a small slip into the sustentaculum tali and by a wide expansion obliquely across the sole into the three cuneiform and the cuboid bones, as well as the bases of the second, third, and fourth metatarsal bones. The sheath of its tendon is 7 to 9 cm. in length and extends about 6 cm. above the malleolus.

The posterior tibial tendon itself may show variants, such as partial duplication or more proximal division into its fasciculi of insertion; it occasionally inserts into the flexor digitorum longus or may join the tendon of the peroneus longus in the sole.

The anomalous tendon described by Le Double lies superficial and anterior to the major portion of the tendon and is inserted into the same regions. Le Double

6. Quain, J.: Elements of Anatomy, Ed. 11, New York, Longmans, Green & Co., 1923, pp. 263-264.

considered the tibialis secundus muscle as a vestigial muscle of the deep layer arising from the posterior aspect of the tibia below the tibialis posticus. The tendon closely accompanies the tendon of the tibialis posterior in the same compartment to the ankle, where it is inserted into the lower part of the anterior annular ligament of the ankle. The tendon of the flexor accessorius longus, when present, occupies the same synovial sheath as does the tendon of the tibialis posticus.

TREATMENT

Eight of our patients were treated conservatively with roentgen rays. One of these patients experienced increase in pain but later responded to adhesive-tape

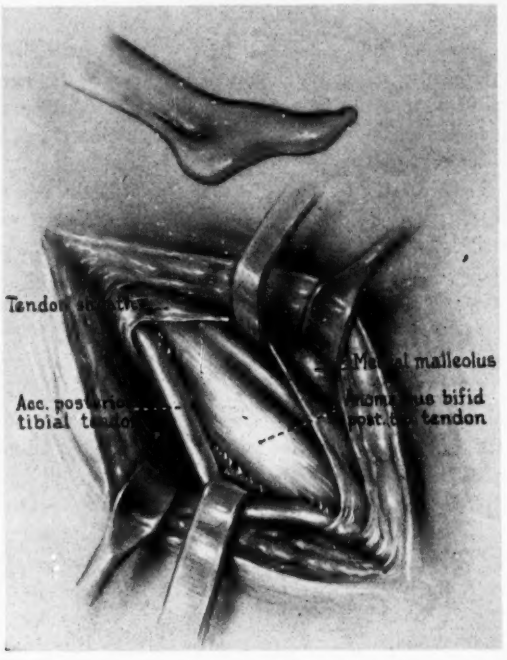

Fig. 1.—Unusually large, partially divided, posterior tibial tendon and an additional posterior tibial tendon, all within the sheath of the posterior tibial tendon.

strapping of the ankle, with gradual recovery in a year. The remaining four conservatively treated patients in whom follow-up studies were available experienced almost immediate improvement and were fully recovered eight weeks later. Two additional patients were advised to have such treatment but refused; one of these patients recovered gradually in three months, and the course of the other untreated patient is unknown.

Eleven of the patients received surgical treatment. Six of them recovered in from one to three months; the average postoperative period of disability was two months. Another patient did not state the time required for recovery but did state that recovery occurred gradually in less than a year; another patient, who had considerable postoperative reaction for which he received roentgen therapy, grad-

ually recovered in a year. In this instance, closure of the tendon sheath had been done. One patient stated that he was not improved eight months after surgical unroofing of the tendon. Both posterior tibial tendons had been affected in this patient. However, the tendon that was surgically treated, the left, was the more

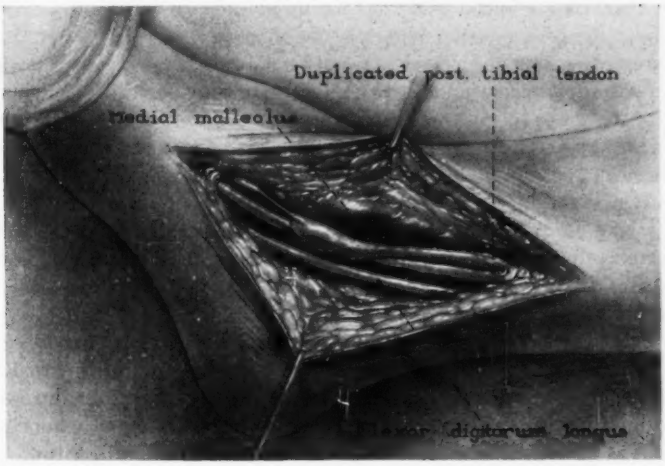

Fig. 2.—Bifid posterior tibial tendon with almost complete rupture of the accessory portion at its distal end.

Fig. 3.—Bifid posterior tibial tendon.

diseased; the tendon on the right side was asymptomatic when the patient was seen at the clinic. Two patients reported that they had been completely relieved of their previous pain in the immediate postoperative period, although discomfort of a different nature was present in the operative region.

In all cases the sheath of the tendon was opened through an incision over the course of the posterior tibial tendon. In every case the sheath was noted to be variably thickened, and the synovial membrane was inflamed to a varying degree. An excessive amount of synovial fluid was present in all cases.

In 4 of these 11 operative cases, anomalous tendons were found within the posterior tibial compartment. The exact nature of these variations can be determined only if the entire course of the tendon is dissected.

In three cases both the posterior tibial tendon and the accessory tendon functioned as posterior tibial tendons. In one instance the added tendon functioned as a flexor of the toes. In the three cases in which duplication of the posterior tibial tendon was present, the secondary tendon appeared to be the anomaly; it was of relatively small diameter and lay anteromedially on the major portion of the tendon. In two instances the secondary tendon was not completely separated but was actually more of a bifid posterior tibial tendon. In one instance this anomalous tendon had been severely ruptured. The major portion of the posterior tibial tendon appeared in these cases to be of greater diameter than normal. These conditions are pictured in the accompanying illustrations (Figs. 1, 2, and 3).

The treatment elected in these cases was excision of the accessory tendon in addition to incision of the sheath of the tendon. This procedure increased the relative diameter of the sheath in its relation to the tendon and resulted in relief from irritation on a mechanical basis. In the case in which the second tendon appeared to function as a flexor of the toes, surgical treatment was limited to unroofing the sheath of the tendon.

SUMMARY

Synovitis of the posterior tibial tendon is an uncommon condition. Generally, the condition responds to rest and roentgen therapy. When the condition does not respond to conservative treatment, surgical measures are indicated.

In 4 of 11 cases with surgical treatment at the Mayo Clinic from 1935 to 1951, inclusive, definite anomalies within the sheath of the posterior tibial tendon were encountered. In three of these cases, the anomaly was that of duplication of the posterior tibial tendon, either partial or complete.

Surgical cure was achieved by an enlargement of the sheath of the tendon by incision and by partial or complete excision of the duplicated tendon when present. In three of the cases in which anomalies were present, complete relief of symptoms was noted. In the fourth, pain persisted, but to a much less severe degree.

THE SURGICAL TREATMENT OF CUSHING'S SYNDROME

Report of One Case and General Considerations

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INVESTIGATION in recent years has shown that the symptom complex previously known as Cushing's disease [1] is not a distinct pathological entity but rather a clinical picture better termed Cushing's syndrome because it most probably can originate from multiple primary etiologies. The existent disorders are metabolic and somatic, the latter being quite striking as a general rule. The syndrome commonly consists of hypertension, diabetes, facial and body contour changes, hirsutism, acne, and amenorrhea or loss of libido. The direct cause of the symptoms is hormonal overproduction by the cortical cells of the adrenal gland or adrenal cortex tumor cells.

We have had experience with one particular case which illustrates well the complexities of treating this entity, and we believe that its report will aid in standardizing treatment.

REPORT OF CASE

The patient (Fig. 1), a 25-year-old woman, delivered a normal child on April 13, 1950, after a pregnancy complicated only by a somewhat excessive weight gain and more than usual ankle swelling near term. The patient's normal weight had always been 120 lb. (54 kg.), and her weight after delivery was 150 lb. (68 kg.). Concerted efforts to reduce were unsuccessful, and she complained occasionally of vertigo. In early December, 1950, increased swelling of the face was noted, and she had spells of generalized numbness. Amenorrhea occurred, and depression of mood became apparent. Because of bradycardia and the swollen face, myxedema was suspected, but it was ruled out by appropriate laboratory tests. Progressive mental depression dominated the picture, and a diagnosis of postpartum depression was made. During the first two weeks in January, 1951, nine electroshock treatments were given with only slight improvement of the mental status. At this time hirsutism, acne, and a refractory diabetes appeared. She returned home, where efforts to control the diabetes were made. The hypertension, virilizing changes, weakness, and mental depression progressed.

On May 25, 1951, she entered St. Joseph's Hospital in Denver. She was very apathetic, bedfast because of weakness and unable to give her own history. She was receiving 65 units of NPH Insulin daily. Physical examination disclosed the typical flushed "moon face" (Fig. 2), hirsutism, acne, "buffalo hump," protuberant abdomen, purplish striae on abdomen and hips (Fig. 3), relatively small extremities, numerous ecchymotic spots, clitoris of normal size,

From the Department of Surgery, University of Colorado School of Medicine.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 5, 1952.

1. Cushing, H.: The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), Bull. Johns Hopkins Hosp. **50**:137, 1932.

blood pressure 152/126, and pulse of 72. Laboratory tests showed red blood cells 5,020,000; hemoglobin 16 gm.; fasting blood sugar 136 mg. per 100 cc. The urine contained sugar (3+) and a trace of albumin; 17-ketosteroid excretion was normal. Serum sodium was 146 mEq. per liter, and potassium was 3.9 mEq. per liter. Roentgen examinations showed a normal skull and sella turcica, and generalized osteoporosis of the skeleton. Subsequent examinations showed normal intravenous and retrograde pyelograms.

A diagnosis of Cushing's syndrome was made. The immediate preoperative preparation was carried out, 25 mg. of corticotropin (ACTH) being given every six hours, and 50 cc. of aqueous adrenocortical extract the day prior to surgery. On the morning of the operative day 1,000 cc. of dextrose in isotonic sodium chloride solution containing 15 units of regular insulin and 50 cc. of aqueous adrenocortical extract, was given. Thiopental (Pentothal) induction with endotracheal administration of nitrous oxide-oxygen-ether was used for anesthesia. The abdomen

Fig. 1.—Appearance of patient several months before onset of disease.

was opened through an upper midline incision. Exploration for a tumor of the adrenal glands or other tumor gave negative results, and a bilateral adrenal hypertrophy was diagnosed. Because of kyphosis and obesity, the wound was exceedingly deep, making exposure difficult and inadequate. An estimated three-fourths of each adrenal gland was removed, with hemostasis proving to be somewhat difficult. The blood pressure was maintained during surgery by the administration of blood, aqueous adrenocortical extract, and epinephrine.

The adrenal tissue removed was reported by the pathologist to show hyperplasia of the adrenal cortex, with nodular distribution of the abnormal cells.

The postoperative course was quite stormy, with frequent episodes of hypotension. The patient was adequately maintained with appropriate doses of aqueous adrenocortical extract, desoxycorticosterone, epinephrine, and saline. After the fourth postoperative day insulin was no longer necessary. On the 10th postoperative day pleural effusion was found on the left side, and 700 cc. of bloody fluid was removed. The etiology of this condition could not be ascertained. On the 12th postoperative day a mild episode of pulmonary edema resulted from excessive administration of

desoxycorticosterone. Reduced dosages and digitalization brought prompt recovery. On the 17th postoperative day the adrenocortical extract was discontinued after gradual daily reduction in dosage.

The patient's strength gradually returned; hirsutism receded, and the blood pressure remained in normal range. On the 65th postoperative day the first menstrual period occurred, and it was of normal duration and flow. The acne was the most refractory symptom, but intensive local dermatological treatment, supplemented finally by parenteral estrogenic substance, brought clearing.

Fig. 2.—Appearance at time of admission to hospital on May 25, 1951.

Gradual improvement occurred, with normal menstruation until January, 1952, at which time recurrence of symptoms at a rather rapid rate became apparent. On Feb. 11, 1952, the patient was readmitted to the hospital for irradiation of the pituitary gland. She was markedly depressed, having bouts of excitement and visual and auditory hallucinations along religious lines. Suicide was mentioned by the patient, so precautions were taken. Irradiation of the pituitary body was given in divided doses, a total of 2,000 r being given. This brought very rapid and remarkable improvement of the mental symptoms in a few days but did not appreciably alter the metabolic or somatic findings.

The entire symptomatology progressed, and on June 2, 1952, the patient was readmitted to the hospital for reoperation. After preoperative preparation with cortisone as outlined by Huggins

and Bergenstal [2] she was operated on, June 7, 1952. The anesthetic procedure was the same as at the first operation. The patient was placed on the table on her right side, and a left posterolateral incision was made, with resection of the 12th rib. The total remaining adrenal tissue, weighing 2 gm., was removed. This remnant was found to be adherent to the posterior peritoneum and not to the kidney. After wound closure the patient was turned and redraped, and the same

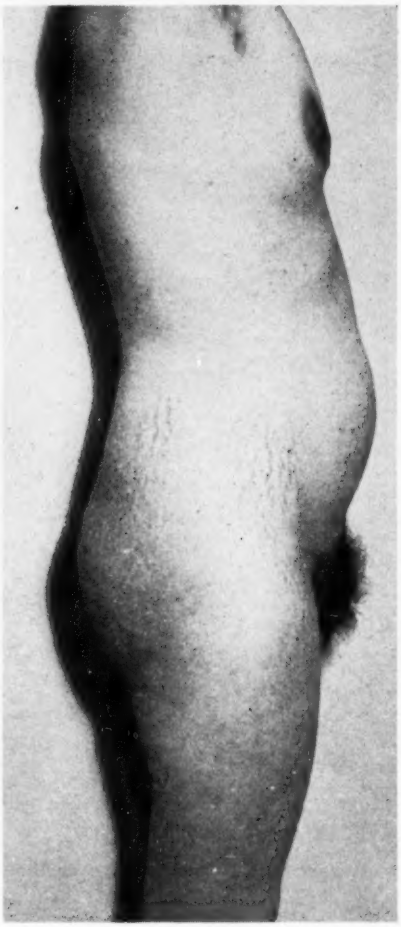

Fig. 3.—Appearance of body on May 25, 1951. Note protuberant abdomen, striae on hips, and atrophic breasts.

incision was made on the right side. Again the adrenal tissue was found adherent to the posterior peritoneum and did not come down with traction on the kidney. A total of 11 gm. of adrenal tissue was removed, leaving a fragment measuring approximately 5 by 7 by 3 mm. in place. This fragment contained attached hemostatic ligatures, and viability was not assured. The pathological diagnosis of the removed tissue was hyperplasia of the adrenal cortices (Fig. 4).

2. Huggins, C., and Bergenstal, D. M.: Surgery of the Adrenals, J. A. M. A. **147**:101, 1951.

The postoperative routine of Huggins and Bergenstal [2] was followed, with the additional administration of a total of 75 cc. of aqueous adrenocortical extract in divided doses intravenously for mild hypotensive fluctuations during the first 24 hours postoperatively. The postoperative course was far smoother than the previous one because this routine rendered the patient quite stable. On the fourth postoperative day a pleuritic type of pain developed in the right chest, which was relieved by adhesive strapping. Pulmonary infarction was strongly suspected, but could not be proved by chest films or clinical course.

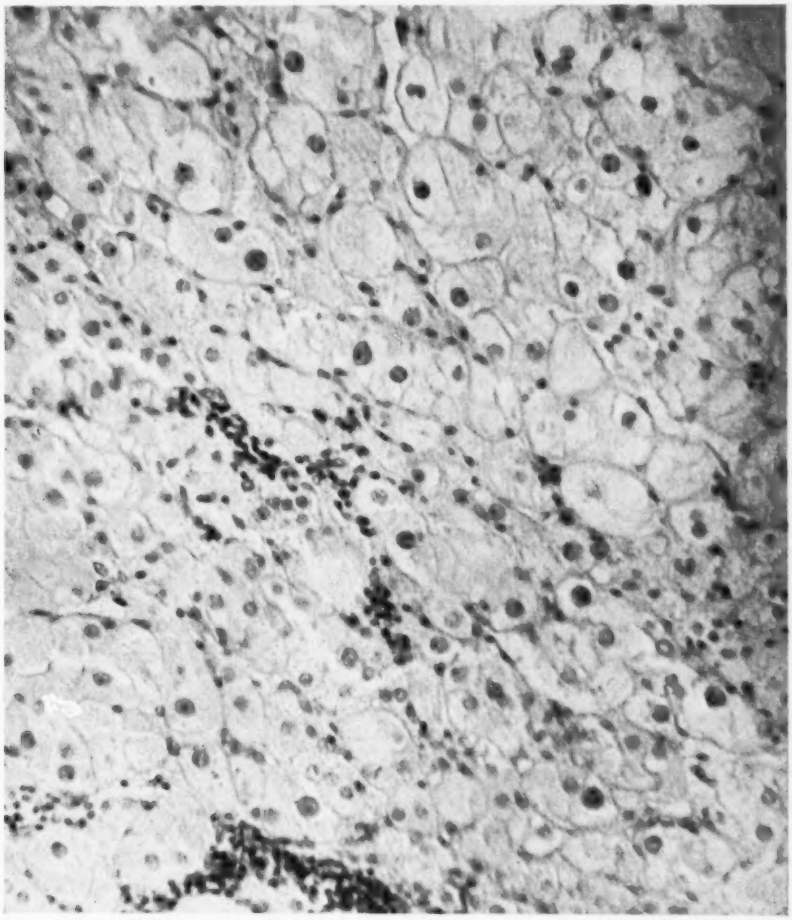

Fig. 4.—Photomicrograph of cortex of adrenal gland removed on June 7, 1952, showing hyperplasia.

She was discharged from the hospital on the 13th postoperative day, when she was taking 40 mg. of cortisone and 1.5 gm. of additional salt by mouth. The urine was sugar free, and her appetite was good. The cortisone has been reduced gradually to the present dosage of 10 mg. per day.

Menstruation began in August, 1952, and has been normal since. Blood pressure and carbohydrate metabolism are normal. Hirsutism and acne are no longer present, and the striations

have faded. Pigmentation over the knuckles has gradually receded. Strength and endurance are optimum, and she maintains her own home and cares for her two children without help. Her face is gradually resuming its former appearance and contour, the most striking change being the return of the previous alert expression of the eyes. Her mental capacity has returned to its former level. The degree of improvement is far greater than that following the first operation.

COMMENT

The transabdominal approach in patients with this body habitus is inferior to the bilateral posterolumbar approach. The preoperative and postoperative routine using cortisone as the basic measure renders the patient quite stable, and when supplemented with salt appears to be fully adequate in replacement. The irradiation of the pituitary gland produced a very marked and rapid improvement in the abnormal mental status even though the metabolic symptoms were not improved. From this case and that of another patient who died of a massive pulmonary embolus in the immediate postoperative course, it might be suspected that the rapid reversal of the bleeding tendency in this disease is a dangerous situation that bears investigation. Apparently less than 14 gm. of adrenal tissue is adequate to produce the full picture of Cushing's syndrome when hyperplasia of the cortical cells exists.

Adrenal Function and Physiology.—The hormones secreted by the adrenal cortex are steroids which have important regulatory action upon (1) electrolyte and water balance, (2) carbohydrate, fat, and protein metabolism, and (3) androgenic manifestations of growth and function.[3] Estrogenic hormones are also secreted but apparently are of less significance except in the cases of feminizing adrenal cortical tumors.[4] Full knowledge of the exact numbers and nature of these hormones is still lacking. However, 28 different steroids have been identified,[5] and it is known that the adrenal cortex is rich in ascorbic acid and lipids.

Apparently the adrenal cortex secretes a small amount of these hormones at a steady rate without apparent external influence.[6] Mainly the secretory activity of the adrenal cortex is dependent on the rate of discharge of corticotropin (ACTH) from the pituitary gland. So far corticotropin is the only substance known to directly stimulate secretions by the adrenal cortex.

The rate of corticotropin release by the pituitary appears to be stimulated by several factors. The blood level of adrenocortical hormones affects this rate of release in an inverse way, a fall increasing corticotropin release, and a rise decreasing its release. Stress, anoxia, or toxins apparently can cause increased release directly. Epinephrine increases corticotropin release by direct and/or indirect action.

The corticotropin probably functions by assisting in the conversion of cholesterol into the corticosteroids of the type which govern electrolyte, carbohydrate, fat, and protein metabolism.[7] The androgenic group of hormones is even less well understood.

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3. Williams, R. H., Editor: Textbook of Endocrinology, Philadelphia, W. B. Saunders Company, 1950, Chap. 4.

4. Simpson, S. L., and Joll, C. A.: Feminization in a Male Adult with Carcinoma of the Adrenal Cortex, Endocrinology **22**:595, 1938.

5. Surgery of the Adrenal Cortex, Editorial, J. A. M. A. **149**:934, 1952.

6. Sayers, G.: Regulation of the Secretory Activity of the Adrenal Cortex, Am. J. Med. **10**:539, 1951.

7. Jacobsen, R. P., and Pincus, G.: The Chemistry of Adrenal Steroids, Am. J. Med. **10**:531, 1951.

The hormones governing electrolyte metabolism are typified by 11-desoxycorticosterone, which controls the blood sodium, potassium, and chloride, and therefore, secondarily, fluid volume. This regulation is accomplished through the renal tubules which reabsorb sodium ions satisfactorily when adequately supplied with the hormone.[8] Conversely, a deficiency results in excessive sodium loss through the kidney with accompanying chloride and water. This change results in transfer of intracellular potassium to the extracellular fluid and renal retention of potassium. Actual potassium intoxication can occur. An excess of the desoxycorticosterone results in sodium and water retention, potassium loss, hypertension, and even pulmonary edema.

The glucosteroids, the second category mentioned above, exert the greatest influence on carbohydrate metabolism.[8] The mode of action of the hormones is apparently catalytic, though the exact mechanism is not well understood, and they do not initiate a primary reaction. The outstanding example of this group is 17-hydroxy-11-dehydrocorticosterone (compound E or cortisone). This hormone promotes the conversion of amino acids to carbohydrate (gluconeogenesis). It suppresses glucose utilization and lowers the threshold for glucose secretion. It increases the mobilization and utilization of fat. It antagonizes protein anabolism. It decreases histamine and histamine sensitivity and increases histaminase. It interferes with many antigen-antibody reactions. It decreases fibroblastic activity and inhibits hyaluronidase. It increases the number and activity of macrophages. It provokes reticulocytosis, erythrogenesis, neutrophilia, eosinopenia, and lymphopenia. It may serve some function in maintaining a normal antithrombin level, since abrupt cessation of its administration after prolonged appreciable dosage may result in increased coagulability of the blood.[9]

A deficiency of the glucosteroids results in the lowering of liver glycogen and of the blood-sugar level, and in decreased appetite. Poor intestinal absorption of glucose is shown by a flat oral glucose tolerance curve. The threshold for hypoglycemic manifestations is lowered. An excess of this hormone results in a reversal of these manifestations and exaggeration of the actions listed in the previous paragraph. The ability to withstand fasting for 24 to 48 hours is a good test for the adequacy of the supply of this hormone.[8]

The androgenic steroids, the third category, are the 17-ketosteroids, of which androsterone and etiocholanolone are the most common examples. Their action is similar to testosterone, but not as potent. Normal urinary 17-ketosteroid content suggests a normal androgenic output of the adrenal cortex. In the female the urinary 17-ketosteroids come almost entirely from the adrenal glands; they are sometimes elevated in Cushing's syndrome, but are usually normal or lowered. Other adrenal steroids may appear in the urine as 17-ketosteroids after alteration at some point in their excretion.

The adrenal cortex apparently secretes a small amount of estrogenic substance.

Pathology.—It is now agreed that the symptom complex of Cushing's syndrome usually results from a hyperfunctioning adrenal cortex. The etiology of this condi-

8. Williams, R. H.: Hyperadrenocorticism, Am. J. Med. **10**:612, 1951.

9. Szilagyi, E. D.; Margulis, R. R., and Jay, G. D.: Observations on Effects of Corticotropin (ACTH) and Cortisone in Management of Some Postoperative Surgical Problems, A. M. A. Arch. Surg. **65**:217, 1952.

tion may be idiopathic oversecretion, primary hyperplasia of the cortex, or secondary hyperplasia.[10] The last may be due to pituitary hyperfunction because of tumor, usually basophilic, or a hypothalamic lesion.[11] The syndrome may result from an adrenal cortex tumor, benign or malignant, or a tumor located along the genital ridge with similar characteristics. Prolonged administration of corticotropin or cortisone will reproduce the characteristic clinical picture.

In primary hyperplasia the location of the initiating abnormality is not known. Exact criteria for establishing the existence of hypertrophy and hyperplasia are still lacking. In one series of cases the weight of the adrenal gland, which was totally removed because of hyperplasia causing symptoms, averaged 15 gm., 7.5 gm. being considered the maximum normal weight.[12] The range of weight in this group was from 6.6 gm. to 21.5 gm. It may well be that future experience will show this figure for the normal weight to be too high. The significance of the microscopic picture of the gland is hard to evaluate, and the areas of hyperplasia are found to be nodular or diffuse.

The lesion may be a tumor, and in this case there is very frequently atrophy or absence of the contralateral gland. In one large series of cases studied, this situation was found 33 times in 46 cases, an incidence of 72%.[13] This same report, which included 104 cases, showed the tumor on the right side in 47 cases, on the left side in 55 cases, and at aberrant sites in 2 cases. The male to female ratio was 1:4. Because of the difficulty in determining the benign or malignant nature of these tumors by histological examination, only an estimation of the percentage of malignancy is possible at the present time. In the series reviewed by Rapaport and his associates, metastases or recurrence developed in nearly 50% of those surviving operation who could be followed. Longmire states that, roughly calculated, 50% of these tumors are malignant.[14] Williams cites a series of 22 adrenal tumors, of which 16 were malignant and 6 benign.[8] Grimson, and his associates report one benign and two malignant.[15] In summary, the incidence of malignancy is probably about 50%.[10]

If the symptoms of Cushing's syndrome appear before the age of 10 years, a tumor is usually present. It is frequently stated that rapid progression of symptoms generally denotes the presence of a tumor. However, from a review of the literature this does not appear to be a trustworthy rule, for there are too many cases which have developed over a period of one and one-half to four years and in which a tumor is present, while many cases of hyperplasia have developed rapidly over a few months.

The incidence of basophilic adenoma of the anterior pituitary as a primary cause is at present undetermined. In the literature of a decade or two ago this factor was

10. Soffer, L. J.: Diseases of the Endocrine Glands, Philadelphia, Lea & Febiger, 1951, Chap. 11.

11. Heinbecker, P.: Cushing's Syndrome, Ann. Surg. **124**:252, 1946.

12. Priestley, J. T.; Walters, W.; Sprague, R. G., and Salassa, R. M.: Subtotal Adrenalectomy for Cushing's Syndrome: A Preliminary Report of 29 Cases, Ann. Surg. **134**:464, 1951.

13. Rapaport, E.; Goldberg, M. B.; Gordan, G. S., and Hinman, F., Jr.: Mortality in Surgically Treated Adrenocortical Tumors, Postgrad. Med. **11**:325, 1952.

14. Longmire, W. P., Jr., and Barker, W. F.: Operations on the Adrenal Glands, California Med. **77**:121, 1952.

15. Grimson, K. S.; Emlet, J. R., and Hamblen, E. C.: Diagnosis and Management of Tumors of the Adrenal Gland, Ann. Surg. **134**:451, 1951.

emphasized. Currently one sees few cases reported, and too often the descriptions of the adrenal glands are insufficient for safe conclusions. While it does occur, it must represent a small fraction of the cases.

The changes described by Crooke [16] are found in the pituitary in the majority of cases of hyperadrenocorticism, whether due to hyperplasia or tumor. These changes are cytoplasmic hyalinization of the basophilic cells, disappearance of the basophilic granules, excessive vacuolization of the cells, ballooning of the nuclei, and general enlargement of the cells. When a basophilic adenoma is found, these changes are absent from the cells of the tumor. It is interesting to note that similar changes occur in the pituitary with overdosage of cortisone in the therapy of other diseases.[17]

Clinical Manifestations.—The picture is very characteristic and striking because of the facial and bodily changes. The face becomes rounded because of fullness of the cheeks and the double chin. It has been aptly termed a "moon face." There is increased circumference of the neck and fullness in the cervicodorsal area because of the "buffalo hump" fat pad in that area. Dorsal kyphosis accentuates this feature. The trunk is full, with protuberance of the abdomen, and the arms and legs are strikingly thin by comparison.

Extensive changes occur in the skin. About the face there is acne, hirsutism, and a flushed appearance of the cheeks. Acne is often present on the face and chest. The skin is generally thin and inelastic, with large purplish striae on the lower abdomen and hips. The fat layer is increased in these areas. Many ecchymotic spots are noted because of the increased bruisability.

Weak atrophic muscles are noted generally and may cause the patient to be bedridden.

The skeleton very often shows a generalized osteoporosis with wedging of the vertebrae resulting in dorsal kyphosis. Nerve root pain secondary to this situation is common, and actual pathologic fracture of vertebrae or ribs does occur.

Hypertension is a prominent feature, and cardiac hypertrophy is very often noted. This may progress to dilatation and decompensation. Arteriosclerosis occurs prematurely, and cerebrovascular accidents occur commonly.

Amenorrhea and loss of libido are usual. Enlargement of the clitoris may occur, though usually not. Breasts, vagina, and uterus may atrophy. In the male there is usually impotence, and testicular atrophy has been reported. Renal disturbances and renal calculi occur with increased frequency. Infection is frequent.

The blood picture usually shows mild polycythemia, lymphopenia, eosinopenia, and relative increase in the neutrophiles. Hyperglycemia is the rule, and a diabetic type of glucose tolerance curve is present.

Special Diagnostic Methods.—Several important laboratory tests have already been mentioned which are of value in establishing the diagnosis. In addition to determinations of the electrolytes and the glucose tolerance curve are such procedures as the determination of the urinary 17-ketosteroids and 11-oxysteroids.

16. Crooke, A. C.: A Change in the Basophil Cells of the Pituitary Gland Common to Conditions Which Exhibit the Syndrome Attributed to Basophil Adenoma, J. Path. & Bact. **41**:339, 1935.

17. Laqueur, G. L.: Cytological Changes in Human Hypophyses After Cortisone and ACTH Treatment, Science **112**:429, 1950.

As a general rule in Cushing's syndrome the 17-ketosteroids are not elevated, and they may be low. If they are elevated, a diagnosis of tumor is favored as the etiological factor. A preponderance of the beta fraction also tends to favor this diagnosis. The elevation of the oxysteroids usually occurs in Cushing's syndrome.[18]

In addition to pyelography, retroperitoneal oxygen injection[19] may help to outline a tumor or hypertrophied gland. This procedure may be done safely by inserting the needle at a point just anterior to the tip of the coccyx with the patient in the Sims or the knee-chest position. The fingers may be introduced into the rectum to aid in locating the needle on the anterior surface of the coccyx. Then 500 cc. of oxygen is injected for each side, and the x-ray pictures are taken one-half and one hour after injection. The patient lies in the prone position with the head of the table elevated 15 degrees. Discomfort is minimal, and no serious reaction has been reported even though the procedure has been done in a very large number of cases. This technique is apparently far safer than perirenal air insufflation. It will often aid in demonstrating and localizing a tumor, but must not be relied upon to rule out hyperplasia as the cause of the disease.

Differential Diagnosis.—The essential problems of differential diagnosis have been discussed in the section on pathology. Aside from this problem of hyperplasia versus tumor of the adrenal cortex and the ever-present possibility of primary pituitary disease, it is well to mention the other possibilities that have been known to give this picture. Included among these are arrhenoblastoma of the ovary, aberrant tumor of the testicle, tumors of the thymus gland, and the Morgagni-Morel syndrome.[3] A Cushing's syndrome type picture has been reported during the administration of large doses of salicylates for a prolonged period of time.[20] It is also stated that mild signs may occur in association with a pheochromocytoma. The possibility of corticotropin or cortisone administration as a cause has already been mentioned.

TREATMENT

Several forms of treatment have been used for this condition, including irradiation of the pituitary gland, testosterone administration, bilateral subtotal adrenalectomy, bilateral total adrenalectomy, and of course unilateral total adrenalectomy for tumor. The current trend is toward surgical treatment by a total adrenalectomy on one side with removal of 85 to 90% of the gland on the other side, or total bilateral adrenalectomy. Establishing a definite diagnosis of tumor preoperatively materially aids in planning the surgical attack.

Preoperative Treatment.—There are few surgical diseases in which the preoperative and postoperative care is of so much importance as in Cushing's syndrome. The hormones of the adrenal cortex are absolutely essential for life, and their deficiency is very rapidly felt. A deficiency of the degree to cause an appreciable amount of shock for any sustained period is usually irreversible. Therefore, the essence of management is prophylaxis, with very rapid treatment of early diagnosed

18. Hardy, J. D.: Surgery and the Endocrine System, Philadelphia, W. B. Saunders Company, 1952, Chap. 10.

19. Gershon-Cohen, J.; Levine, S., and Hermel, M. B.: Retroperitoneal Pneumography by Injection of Oxygen into the Presacral Space, Am. J. Roentgenol. **68**:391, 1952.

20. Cochran, J. B.; Watson, R. D., and Reid, J.: Mild Cushing's Syndrome Due to Aspirin, Brit. M. J. **1**:1411, 1950.

deficiency. The change that cortisone has made is well shown by the case described in this article. With cortisone as the base of treatment a patient of relative stability is obtained.

In the presence of the severe metabolic disorders the preoperative preparation must begin early with efforts to restore a positive nitrogen balance by a high protein diet and administration of testosterone,[14] which has an action antagonistic to the hormones causing protein breakdown and gluconeogenesis. The diabetes will be refractory by the usual standards of control, but efforts should be made to furnish adequate insulin to prevent exaggerated rise in the blood sugar. The electrolyte balance should be determined, sodium intake limited, and potassium supplemented, as necessary to bring the patient to surgery without alkalosis, edema, or potassium deficiency. These patients are deficient in resistance to infection; hence antibiotics prophylactically may be indicated. A careful evaluation of the cardiac status should be done to detect failure and to have a base line study for future reference.

When these factors are cared for to the maximum, the immediate preoperative routine becomes paramount. We found the routine of Huggins and Bergenstal [2] eminently satisfactory. This consists of starting use of cortisone, 50 mg. every six hours, on the day prior to surgery and also giving desoxycorticosterone, 5 mg., and sodium chloride, 5 gm. On the morning of surgery one hour prior to operation cortisone, 150 mg., and desoxycorticosterone, 5 mg., are given. During surgery an effort is made to replace blood as it is lost. An additional 500 cc. of isotonic sodium chloride solution is given during surgery. Falls in blood pressure during surgery are treated by the intravenous administration of the aqueous adrenocortical extract and/or arterenol (Nor-epinephrine) and additional blood if this is thought necessary.

Anesthesia.—Premedication and choice of anesthetic agent were for a time considered to be a very specialized problem and accompanied by great risk. A prejudice against the use of morphine existed. One now finds that with the increasing number of persons operated on the preoperative preparation has become adequate enough so that morphine, meperidine, scopolamine, and atropine [21] have all been used successfully in one series or another. Most writers advise using these drugs in reduced dosages so that one could feel safe in using one-half to three-fourths of the usual calculated dose.

The choice of anesthetic agent is not complicated. Huggins and Bergenstal use spinal anesthesia routinely. The Mayo Clinic anesthetists use routine endotracheal intubation with either an ether and oxygen mixture or a thiopental sodium and curare combination intravenously with nitrous oxide and oxygen by inhalation. Our preference is the thiopental induction with endotracheal intubation and nitrous oxide-oxygen-ether. When danger of entering the pleural space exists, the safeguard of intubation seems wise. With this variety of agents to choose from there seems no need to risk the arrhythmias of cyclopropane, especially when a sympathomimetic agent might be required.

The anesthetist must watch the blood pressure and pulse with extraordinary diligence, for the greatest danger in adrenal surgery is shock, which must be treated immediately in the early stage of development or it becomes irreversible rapidly. During surgery he must use blood and intravenous aqueous adrenocortical extract

21. Papper, E. M., and Cahill, G. F.: Anesthetic Problems in Hormonal Disorders of the Adrenal Glands, J. A. M. A. **148**:174, 1952.

as his main measures of support. Arterenol may at times be indicated. In our experience 10 cc. of an aqueous adrenocortical extract, such as eschatin,® will usually bring a prompt response, and this dose may be repeated as often as necessary, for there is no danger in giving reasonably large amounts of this substance. Too often in retrospective consideration at a clinical pathological conference a review of a record indicates the use of too little of this agent in the presence of adrenal insufficiency. With cortisone as a preparatory agent such supportive medication can be held to a minimum.

Operation.—If a tumor has been demonstrated preoperatively and is of appreciable dimensions the transthoracic approach on that side is probably best since it allows the best exposure and probably more adequate surgery for a malignant lesion. The patient is placed on the table in the lateral position and the chest is opened by a posterolateral incision in the 10th interspace. The diaphragm is then opened by an incision in the direction of its fibers, and the tumor is found in the retroperitoneal space. The tumor can be resected, and if necessary the kidney can be removed. The diaphragm should be closed with interrupted mattress sutures of silk. The chest should be closed, with a catheter placed through a separate stab wound and underwater seal suction attached.

In the event a localized lesion is not demonstrable preoperatively, we prefer the incision advocated by Huggins and Bergenstal.[2] In this method the patient is placed on the table in the lateral position, and the table is broken in the middle. The incision is then made over the 12th rib from approximately 1 in. (2.5 cm.) lateral to the spinous processes to about the midaxillary line. The 12th rib is resected and the incision carried through the periosteal bed. The incision is carried through the retroperitoneal fat, and the fascia of Gerota is opened. The perirenal fat is then separated until the kidney and adrenal are located. In our case of reoperation in which we were pursuing a remnant of gland previously subtotally excised, the scarring about the gland caused it to adhere to posterior peritoneum instead of kidney, so that it lay higher and more forward than usual, and, since it was smaller, any less adequate exposure would have made removal most difficult.

In the event that a tumor is not encountered on exposure of the first gland, the plan advocated by Priestley[12] has been shown to be sound. This consists of removing 85 to 90% of the first gland exposed if it is of normal or increased size, and leaving it untouched except for removal of a small biopsy specimen if it is atrophic since this almost always indicates a tumor on the opposite side. The wound is then closed, and, unless there is a specific contraindication, the patient is turned and redraped and a similar incision is made on the opposite side. If a tumor is found, it is removed along with any adrenal tissue found on that side. If there is any adherence to or involvement of the kidney, it should be removed as well. If hyperplasia is present, the entire gland on this side is removed. In anticipation of turning the patient, it is best to do a cut down on the saphenous vein preoperatively and to introduce a polyethylene catheter for fluid administration.

Postoperative Treatment.—Following operation, cortisone, 50 mg., is given every four hours.[2] Hypotensive episodes are treated as during surgery. On the day following surgery cortisone can be reduced to 50 mg. every six hours and desoxycorticosterone, 5 mg., is given. Daily supplement of 3 gm. of salt is given by mouth or intravenously depending on the status of the patient. On the second

day the cortisone is reduced to 50 mg. every 12 hours and the desoxycorticosterone is given only if needed. The salt intake is 3 gm. On succeeding days the cortisone is reduced gradually, depending on what procedure was carried out. If a tumor was removed, it is reduced gradually until it is discontinued on the fifth to the seventh day. If a total removal of gland was done on one side and a subtotal removal on the other, the dosage of cortisone is gradually reduced until normality can be maintained without it. If a total bilateral adrenalectomy was done, the reduction is continued until about 7 to 10 days, when the maintenance dose is established usually between 25 and 50 mg. daily. If only one gland was partially removed in a two-stage procedure, no cortisone need be given postoperatively as a rule. It must always be remembered that cortisone administration must not be stopped abruptly and that there is a lag period between administration and final effect probably of about four days. If a total bilateral adrenalectomy has been done, the patient can be maintained without desoxycorticosterone supplementation if 3 to 5 gm. of additional salt is given daily.[2]

After operation the patient may experience periods of anorexia, nausea and vomiting, weakness and electrolyte imbalance. These may represent indications of inadequate cortisone dosage or an excess dosage, and should be treated accordingly.

Our experience leads us to feel that special precautions should be taken to prevent thromboembolic disease. Antibiotic and vitamin administration should be given as deemed necessary.

SUMMARY AND CONCLUSIONS

Cushing's syndrome due to tumor or adrenocortical hyperactivity is amenable to surgical treatment.

When it is due to adrenocortical hyperplasia, inadequate removal of tissue results in recurrence of Cushing's syndrome.

We prefer total adrenalectomy on one side and a radical subtotal removal on the second side.

Pituitary irradiation gave striking improvement of the abnormal mental symptomatology during an active phase of the disease in one case.

Transthoracic approach is preferred for a demonstrable tumor.

We prefer bilateral posterolateral incision with resection of the 12th rib in operation for hyperplasia of the adrenal cortex.

Resection of both adrenals at one operation is a satisfactory procedure.

DISCUSSION

DR. EDWIN M. MILLER, Chicago: I wish to speak briefly on the question of the surgical approach for the removal of adrenal tumors. While it is true that the posterolateral route is the one most frequently used, and that the transthoracic approach has a definite advantage in some cases, I believe that the abdominal route through a long transverse incision just above the level of the umbilicus should not be entirely ignored. In fact, it has some points in its favor that the others do not possess.

Within the past two years we have successfully removed two adenomas of the adrenal cortex in cases of typical Cushing's syndrome, one on the right and the other on the left side, each about the size of a large walnut, using the abdominal route. The three lantern slides which I am now showing will illustrate very well the gross appearance of these tumors and also the technical procedure involved in their removal.

On the right side the duodenum is mobilized and reflected medially just as if one were going to explore for a stone in the pancreatic portion of the common duct. The posterior peritoneum is

incised as far upward as possible toward the diaphragm; the inferior vena cava is retracted medially and the common duct upward, thus permitting a good exposure of the upper pole of the kidney and the adrenal tumor, which in this instance was easily removed.

On the left side the procedure is slightly more difficult. After the entire gastrocolic ligament has been widely divided, the transverse colon is retracted downward. The posterior peritoneum is incised along the lower border of the pancreas, and the body and tail of the pancreas (together with the spleen if necessary) are elevated and reflected medially, allowing one to easily expose the left adrenal. If this is done merely for exploration in order to verify the presence of a normal adrenal, it can be accomplished in a few minutes' time; if it is undertaken for the removal of a tumor (as in our case), this can be accomplished without too much difficulty.

In addition, this approach allows one to inspect and palpate the pelvic organs, and to explore for accessory adrenal rests, and it saves considerable time, a factor quite important when the patient is not a good surgical risk.

Dr. Marvin E. Johnson, Denver: I want to thank Dr. Miller for his comments. Using the transverse abdominal incision is far better than the vertical type of incision. It is our experience that the average patient has quite a bit of kyphosis and a great deal of obesity, and we have had considerable trouble in the abdominal approach, and find that the posterior approach is easier.

In the case of a large tumor, however, that can be demonstrated by x-rays preoperatively, we are inclined to use the transthoracic approach, going through the 10th interspace and opening the diaphragm.

SUBSTITUTION OF THE EXCLUDED RECTOSIGMOID COLON FOR THE URINARY BLADDER

Preliminary Report

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TOTAL cystectomy, for primary or metastatic carcinoma of the urinary bladder, with anastomosis of the ureters into the intact colon, is a procedure that is, at best, only reluctantly recommended by urologist and surgeon and similarly accepted by the patient.

USUALLY ACCEPTED REASONS FOR DELAYING TOTAL CYSTECTOMY WITH URETEROSIGMOIDOSTOMY

Many factors militantly array themselves against ready, free, earlier, and more universal employment of the procedure. It has long been known among urologists, and generally accepted by them, that the papillary type of vesical carcinoma is an entity which lends itself to amelioration, if not cure, by the less formidable attack of repeated fulguration, sometimes over a period of many years. It has been generally agreed, however, that the infiltrative type of carcinoma is a much more resistant lesion, failing to respond to roentgen therapy, interstitial radiation, or fulguration, or to a combination of these, and it is in this type of carcinoma that radical cystectomy with ureteral diversion is usually, or at least more frequently, employed. The immediate or late probability of the occurrence of a chronic hyperchloremic acidosis, characterized clinically by anorexia, nausea, vomiting, malaise, thirst, and diarrhea, mirrored in the chemical pattern of the blood by elevation of the chlorides, urea, and nonprotein nitrogen, with depression of the plasma bicarbonate, is a further deterrent to more vigorous and radical intervention. The work of Ferris and Odel [1] and Boyce and Vest [2] demonstrated forcibly in their chemical studies of the blood in persons who had undergone bilateral ureterosigmoidostomy the very high incidence of postoperative chronic acidosis, since it occurred in 79% of their patients.

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 5, 1952.

1. Ferris, D. O., and Odel, H. M.: Electrolyte Pattern of the Blood After Bilateral Ureterosigmoidostomy, J. A. M. A. **142**:634, 1950.

2. Boyce, W. H., and Vest, S. A.: The Role of Ammonia Reabsorption in Acid-Base Imbalance Following Ureterosigmoidostomy, J. Urol. **67**:169, 1952.

A procedure, the employment of which may well relegate four out of five patients to a precarious and debilitated existence, cannot, perforce, be accorded the same enthusiasm that is given colectomy for carcinoma of the colon or abdominoperineal resection for malignant disease of the rectum. The search for a therapy in bladder carcinoma which promises a brighter future for the patient rightfully continues to concern everyone.

DEBILITATING SEQUELAE FOLLOWING IMPLANTATION OF THE URETERS INTO THE INTACT COLON

Hyperchloremic acidosis is due, probably, to no single factor, but rather to a multiplicity of factors, among which may be mentioned urinary tract obstruction [3] resulting from shunting the urine from the urinary bladder, a low-pressure reservoir, where average intravesical pressure is 8 to 10 cm. of water rising to 130 cm. at micturation, to a high-pressure reservoir, the rectum, with an average pressure of 27 cm. of water,[4] increasing at defecation to as much as 270 cm. of water. Too, there is the very great likelihood of ascending, intraluminal, ureteral or periureteral, lymphatic infection with intermittent exacerbating pyelonephritis and eventual chronic renal suppression. Of import, also, may be the excessive resorption of chlorides, probably as ammonium chlorides, from the colon. That this absorption occurs principally from the colon proximal to the sigmoid has been pointedly indicated by Boyce,[5] who showed that in animals in which vesicosigmoidostomy had been done electrolyte imbalance was promptly corrected when proximal colostomy was established.

METHODS OF URETERAL IMPLANTATION

The urologic literature is replete with multitudinous methods of implanting the ureters into the intact colon, each variable of the sundry techniques having for its goal the minimizing of infection, obstruction, renal damage and acidosis. More than 70 different methods of ureterointestinal anastomosis have been proposed. Their very multiplicity is an admission that the ultimate is yet to be reached.

ROLE OF PERMANENT FECAL-STREAM DIVERSION

It has seemed not improbable to us, as suggested by Mauclaire [6] in 1895 and Kröenig [7] in 1907, that if a fecal-free urinary reservoir to which the urine could safely be diverted were provided, accompanied by complete, urinary control, infection, renal damage, and chronic acidosis might be minimized and rehabilitation of the patient with bladder carcinoma more nearly achieved. The unqualified acceptance by patient and surgeon of permanent colostomy, where complete sacrifice of

3. Sauer, H. R.; Blick, M. S., and Buchwald, K. W.: Changes in Renal Function Following Ureteral Transplantation, Surg., Gynec. & Obst. **89**:299, 1949.

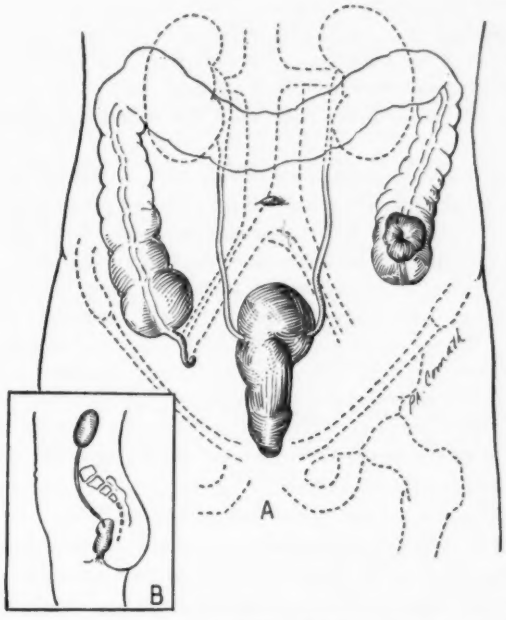
4. Hurst, A. F.: Constipation and Allied Disorders, a Monograph, London, Frowde, 1919.

5. Boyce, W. H.: The Absorption of Certain Constituents of Urine from the Large Bowel of the Experimental Animal (Dog), J. Urol. **65**:241, 1951.

6. Mauclaire: De quelques essais de chirurgie expérimentale applicables au traitment: De l'exstrophie de la vessie; Des abouchements anormoux du rectum; Des anus contre nature complexes, Cong. français de chir., 546-552, 1900, cited by Papin, 1925.

7. Kröenig: Die Anglegung eines Anus praetera-naturalis zur Vermeidung der Colipyelitis bei Einpflanzung der Ureteren ins Rectum, Zentralbl. Gynäk. **31**:559-561, 1907.

the rectum and anus is necessary for low-lying carcinoma, has motivated us in the thought that patient and urologist might, with equal equanimity, accept colostomy if more complete restoration of the victim of vesical carcinoma could be thereby attained. Accordingly, in eight patients, seven of whom had primary carcinoma of the bladder and one whose bladder was invaded secondarily by squamous cervical carcinoma, total cystectomy was performed with the establishment of permanent midsigmoid colostomy for complete diversion of the fecal stream and implantation of the ureters into the distal sigmoid colon after closure of its proximal end. In each instance the operation was completed in one stage.



A, illustrating diagrammatically the proximal colostomy and the excluded rectosigmoidal pouch with ureters implanted into it. *B*, sagittal section showing new urinary reservoir with continent anal sphincter furnishing excellent control of urine.

SURGICAL MANAGEMENT

Preoperative Preparation.—Complete evaluation of the blood with respect to its total volume and chemical constituents is mandatory. Restoration of blood volume and correction of electrolyte imbalance are carefully sought. For a period of at least five days before operation a high-caloric low residue oral intake, with the ingestion of 4 gm. of sulfasuxidine powder, is maintained.

Type of Anesthesia.—In most instances, unless contraindicated, spinal anesthesia has been used. The profound segmental subumbilical relaxation, so essential to accurate unhampered dissection, is thus made more readily and safely available to the surgeon.

Type of Incision.—A long midline, extending well above the navel, or a generous transverse incision have been employed with equal facility, and postoperative healing has been satisfactory in both.

Ligation of Internal Iliac Arteries.—As soon as operability has been established, ligation of both internal iliac arteries is done just below the common iliac trunk. This has greatly minimized blood loss in an otherwise ordinarily vascular dissection and has greatly expedited the procedure. The ureters are divided 3 in. (7.6 cm.) from the bladder and in the male en bloc removal of the bladder, prostate, seminal vesicles, and ductus deferens accomplished, the dissection encompassing a wide area of paravesical tissue as well.

Establishment of Permanent Colostomy.—The midsigmoid colon level is sought and the bowel divided at that point. The proximal stump is brought out, dependent usually on the length of the mesentery, wherever tension is minimal. This has most frequently been at or near the navel, and we have noted that postcolostomy care of our patients is less troublesome than when the stoma is near the left anterior-superior iliac spine.

Construction of Urinary Reservoir.—The proximal end of the distal sigmoid colon is inverted with three layers of 000 chromic absorbable surgical (gut) sutures, making a blind pouch of the distal rectosigmoid colon about 20 cm. in length. Bilateral ureteral implantation into this distal rectosigmoidal pouch is done by the simple end-to-side method with two layers of 000 chromic gut. Through-and-through sutures penetrating all coats of bowel and ureter are used. No attempt has been made to use the "mucosa to mucosa" technique, and no leakage of urine has occurred. We feel strongly that far too much attention has been paid to variegated methods of anastomosis and much too little attention has been directed to the underlying basic principles of healing, which are dependent essentially on an adequate blood supply of the united viscera and minimal tension upon the suture line.

Abdominal Closure.—This is done in layers with an advantageously placed Penrose drain to forestall serosanguineous pocketing in the pelvis.

Postoperative Care.—Serious problems in fluid and electrolyte balance have not occurred either immediately or later. Frequent estimations of blood volume and electrolyte studies to evaluate sodium, potassium, calcium, chloride, urea nitrogen, plasma bicarbonate, and nonprotein nitrogen content of the blood are made. Usually, 3,000 cc. of parenteral fluids given daily have sufficed to maintain adequate fluid balance. At the end of 48 hours the clamp on the proximal colon is removed, followed by resumption of colon motility in two or three additional days. Accumulated urine in the rectosigmoidal pouch is drained every two hours by rectal tube for the first few days. Thereafter the patient is urged to "void" from the rectum every two hours. At the end of two weeks, control of urine by the anal sphincter is excellent.

COMMENT

In seven of the eight patients in whom one-stage cystectomy, proximal colostomy, and ureteral anastomosis with the excluded, distal sigmoidorectal segment have been done, ascending ureteritis and pyelonephritis have not been seen and hyperchloremic acidosis with renal suppression has been, with one exception, notably absent to date. The only patient exhibiting mild hyperchloremia and postoperative acidosis was, interestingly, the sole one (E. L., Table) in whom obvious preopera-

tive pyelonephritis was definitely present. This solitary acidotic sequel is in accord with the clinical experimental work of Lapides,[8] who observed that resorption of urinary constituents occurred in some degree in perhaps all patients submitted to ureterosigmoidostomy but that hyperchloremia and acidosis resulted only when renal damage coexisted.

Eventual renal damage following ureterosigmoidostomy in the usual fashion ensues most frequently as a result of repeated infection of the kidneys. The occasion for this infection, it is universally agreed, is the direct implantation of the ureters into the fecal stream. The ascent of infection cannot help but be invited by this conventional method, and the search for a relatively clean urinary reservoir has

Summary of Data

Patient	Age, Yr.	Sex	Diagnosis	Operation	Date	Result
H. U.	51	M	Transitional cell carcinoma of posterior bladder wall	Permanent colostomy; total cystectomy; ureterosigmoid anastomosis, one-stage	5/20/50	Alive 11/15/52; suspect recurrence, but no hyperchloremia or acidosis
T. S.	59	M	Squamous cell carcinoma of bladder	Permanent colostomy; total cystectomy; ureterosigmoid anastomosis, one-stage	5/ 5/51	Died 8/1/51; recurrence; no hyperchloremia or acidosis
L. R.	46	F	Metastatic squamous cell carcinoma of bladder secondary to carcinoma of cervix	Permanent colostomy; total cystectomy with resection of vagina; ureterosigmoid anastomosis, one-stage	12/14/51	Died 11/20/52 of extensive hepatic and abdominal metastases; not even terminal hyperchloremia or acidosis occurred
L. S.	61	F	Squamous cell carcinoma of bladder with invasion of the vaginal septum	Permanent colostomy; total cystectomy; total hysterectomy and resection of upper ⅔ of vagina; ureterosigmoid anastomosis, one-stage	3/10/52	Alive and well; no hyperchloremia or acidosis
R. S.	46	M	Squamous cell carcinoma of bladder	Permanent colostomy; total cystectomy; ureterosigmoid anastomosis, one-stage	6/ 1/52	Alive and well; no hyperchloremia or acidosis
E. L.	71	M	Squamous cell carcinoma of bladder, Grade I	Permanent colostomy; total cystectomy; ureterosigmoid anastomosis, one-stage	4/26/52	Bilateral pyelonephritis with renal and hepatic insufficiency present before operation; patient exhibits hyperchloremia and acidosis now
J. S.	66	M	Transitional cell carcinoma of bladder	Permanent colostomy; total cystectomy; ureterosigmoid anastomosis, one-stage	7/ 1/52	Alive and well; no hyperchloremia or acidosis
H. W.	54	M	Squamous cell carcinoma of bladder with invasion of iliac nodes	Permanent colostomy; total cystectomy; ureterosigmoid anastomosis, one-stage	11/20/52	Immediate postoperative chemical studies of blood normal

encouraged us to divert the fecal stream and construct the excluded, continent, rectosigmoidal pouch. There has been no immediate postoperative mortality in the eight patients undergoing this procedure. The patients have been followed for from several months to two and one-half years; repeated postoperative urograms have been normal, and recovery and rehabilitation have occurred.

CONCLUSIONS

One-stage cystectomy, permanent sigmoid colostomy with the construction of an excluded rectosigmoid pouch and implantation of the ureters into it, is a safe operative procedure in the management of primary or metastatic vesical carcinoma.

8. Lapides, J.: Mechanism of Electrolyte Imbalance Following Ureterosigmoid Transplantation, Surg., Gynec. & Obst. **93**:691, 1951.

The distressing complications of ureteral obstruction, urinary sepsis, hyperchloremia, and acidosis, so frequently encountered when the ureters are implanted into the intact colon, have been conspicuously absent in our limited experience, and presently apparent satisfactory results may warrant more frequent employment of this technique in the attempt to salvage and reconstitute a greater number of persons afflicted with malignant disease of the urinary bladder.

DISCUSSION

DR. HENRY SWAN, Denver: I should like to compliment Dr. Sauer on the interesting series of patients that he reported on this morning.

In 1942 I was resident at Children's Hospital in Boston, and we had to deal with the problem of fecal and urinary incontinence in children who had myelomeningocele. They were very unhappy children because they had constant dribbling of urine and feces, which made them social outcasts and prevented them from being accepted in school. The problem was a distressing one.

Dr. Lanman, at Children's Hospital, had tried transplantation of ureters into the bowel, then bringing out the bowel as a colostomy. This procedure had one advantage in that it transferred the leaking combined fecal and urinary stream to the abdomen, where there was a much better chance to collect it in a bag and thus maintain the child in a somewhat reasonably social condition. However, this procedure was followed invariably by a very intense ammoniacal odor, so that again these children were unacceptable in school.

It occurred to us to colostomize the rectosigmoid isolated as a separate pouch and into this pouch put the ureters; we then brought out the descending colon as a separate colostomy. Under these conditions, then, we had a urinary colostomy and a fecal colostomy, thus separating the two streams.

This procedure was performed between 1943 and 1945 in about seven patients by Dr. Gross, and I think it was essentially the same urinary setup as you saw in Dr. Sauer's diagrams, i. e., a sigmoid bladder. We now have a six- to eight-year follow-up on these seven patients.

By and large, we felt that the procedure was fairly satisfactory. It certainly rehabilitated the majority of these children. They have gone on in school. The oldest one has recently completed college.

There were some complications of note, but, as Dr. Sauer has found, they were not primarily due to renal dysfunction. None of these children has had serious disturbance of his renal function. One child had Addison's disease and subsequently died in an Addisonian crisis. One child had persistent incrustation of the colon with ammonium salts, the formation of bladder stones in the segment of colon. Another had what was possibly the result of a technical mistake at surgery—a repeating prolapse of the bowel, requiring reoperation.

However, in spite of these annoying complications, renal function has remained good, and we believe with Dr. Sauer that the procedure has merit when one needs to convert the urinary stream with sacrifice of the bladder.

DR. JOEL W. BAKER, Seattle: This thought-provoking original procedure of Dr. Sauer's is very stimulating. From my small experience with cases of this sort, I should like to raise a few questions.

The advantage of the procedure, as Dr. Sauer has mentioned, is to prevent hyperchloremic acidosis and ascending infection, and in so doing the patient is given what would otherwise be an unnecessary fecal colostomy. He has accomplished urinary continence by the anal sphincter.

But it may be that in some older patients, as in one of mine, the anal sphincter will not be as continent for the perpetually secreted liquid urine as for normal feces. One of my patients, a doctor's wife, now aged 85, about five years ago had a total cystectomy done by me for cancer. I transplanted the ureters in the normal way, into the sigmoid, not with a colostomy. She has remained well, and the disease so far is arrested, but she has incontinence of the anal sphincter so that she suffers from urgency by day and has to wear a diaper at night.

I mention this because it might be, Dr. Sauer, that in some of these older patients the continence may not be as good.

Contrast that with two patients in whom I have deemed it justifiable to do a pelvic viscerectomy for carcinoma of the rectum that had invaded the base of the bladder, without distant metastases demonstrable. These two patients have had very satisfactory results with the Bricker procedure; i. e., using an isolated loop of terminal ileum, closing one end of this isolated loop, transplanting the ureters into this loop, and then bringing the other end of the loop out and applying a Rutzen bag. These patients even boast of how easy it is for them to get in and out of a toilet to empty their "bladder."

It has the advantage that it also is an isolated loop and therefore should be relatively sterile and reduce the incidence of ascending infection. It also had a greater advantage, it seems to me, in that the urine is immediately propelled outward into an artificial outer bladder, rather than lying in an inner bladder, as the rectum, and there is therefore even less chance for resorption of chloride and hyperchloremic acidosis.

These two patients have been very happy. Of course, they had to have a colostomy for feces on one side and a Rutzen bag on the other, since a pelvic viscerectomy was required.

I should like to ask Dr. Sauer (and I know he is familiar with this work of Bricker) whether he thinks this substitution of an isolated loop of ileum might be preferable to using the rectum and creating a colostomy.

I might say, facetiously, that Dr. Sauer has transferred the male patient into a female's habits in the toilet, which I am sure here in Texas would be bad.

DR. DEAN SAUER, St. Louis: I should like to thank the discussers for their informative and provocative remarks.

(Slide) The colostomy in this patient is essentially a much "drier" colostomy than one finds when the urinary stream is not diverted to the rectum. I cannot explain it, but we have observed universally that these patients in whom we have excluded the rectosigmoid and have implanted the ureters therein have had much drier colostomies than any other type of patient upon whom we have operated.

Urinary continence is something that I think is gained over a period of time, usually in about two weeks. Dr. Baker, I certainly can appreciate that one would have to be somewhat cautious, especially in very old persons, in unqualifiedly recommending this procedure.

The reason we have felt it does have a place might be summed up in one sentence: Ascending ureteral infection and pyelonephritis does not result, and the relatively clean urinary reservoir seemingly offers the patient rehabilitation without infection, without acidosis, and without debilitating sequelae.

I certainly want to observe these patients over a very long period of time, because we know that in some persons hyperchloremic acidosis occurs as late as 20 years after ureterosigmoidal anastomosis. I do not believe that anything except time and continued observation and effort will give us a better answer to the problem than the one we have at present.

ELECTROLYTE LOSS BY POSTOPERATIVE NASAL-GASTRIC SUCTION

FREDERIC W. TAYLOR, M.D.
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THE MOST valuable single addition to the surgical armamentarium in recent times is the nasal-gastric suction tube. Its general acceptance in postoperative care has become so commonplace that little thought is given to the possible dangers and accidents which may result from its use. It is the purpose of this discussion to evaluate some of these possibilities to see whether they are real or imagined.

Many isolated studies have been made which indicate the amount of electrolyte and fluid lost with nasal-gastric suction.[1] To my knowledge no broad clinical study has been carried out to demonstrate the average amount of this loss in hospital patients. It seemed desirable to investigate this particular phase of electrolyte balance in the average clinical application of the gastric tube. It is important to know just how much fluid is usually removed from the patient by this route and the amount of electrolyte that might be expected to be removed with it.

Of equal interest and importance is a point which has been argued frequently on surgical rounds and with our medical confreres. This concerns the practice of allowing the postoperative patient to drink as much water as he wishes so long as his gastric suction tube is functioning properly. Those who advocate this practice feel that only a given amount of electrolyte may be removed from the stomach and that bathing the gastric mucosa with tap water does not increase the loss. This routine admittedly keeps the tube in good working order and temporarily pacifies the patient.

Those who oppose this practice indicate that an increased and even dangerous amount of electrolyte may be lost by gastric washing. They also suggest that a patient's thirst can and should be handled entirely by intravenous fluids. If the additional loss is dangerously high, then this feature of postoperative care is certainly of more than experimental interest.[2]

Read at the Sixtieth Annual Meeting of the Western Surgical Association, Houston, Texas, Dec. 5, 1952.

From the Department of Surgery, Indiana University School of Medicine and Veterans Administration Hospital.

1. (*a*) Van Slyke, K. K., and Evans, E. I.: The Significance of Urine Chloride Determination in Detection and Treatment of Dehydration with Salt Depletion, Ann. Surg. **128**:391, 1948. (*b*) Bartlett, R. M.; Bingham, D. L. C., and Pedersen, S.: Salt Balance in Surgical Patients, Surgery **4**:441, 1938. (*c*) Lockwood, J. S., and Randall, H. T.: The Place of Electrolyte Studies in Surgical Patients, Bull. New York Acad. Med. **25**:228, 1949. (*d*) Abbott, W. E.: Review of the Present Concepts on Fluid Balance, Am. J. M. Sc. **211**:232, 1946. (*e*) Dick, V. S.; Maddock, W. G., and Coller, F. A.: Sodium Chloride Content of Gastro-Intestinal Secretions, Proc. Soc. Exper. Biol. & Med. **37**:318, 1937. (*f*) Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, Am. J. Physiol. **93**:407, 1930.

2. (*a*) Footnote 1. (*b*) Taylor, F. W.: Fluid Balance and Sodium Chloride, J. Indiana M. A. **45**:409, 1952.

METHODS

In so far as possible, actual clinical conditions were simulated. The "patient" had been admitted to the Indianapolis Veterans Hospital for study and evaluation of his gastric secretion.[2b] These tests were supervised faithfully though somewhat dubiously by consecutive generations of surgical residents.[3] As a rule the patient had been in the hospital for at least a week before tube aspiration was started. Each patient underwent tests which were divided in two general divisions.

During Part I, nothing was allowed by mouth, whereas water was given freely during Part II. The same person underwent both Part I and Part II and so constituted his own control. On the morning of the test, breakfast was omitted, and a nasal-gastric tube was placed in the stomach. Gastric contents were evacuated and all aspirated fluid was discarded. Constant suction was then applied and allowed to continue for 24 hours. The tube was irrigated each two hours with a small amount of tap water to insure patency.

During this 24-hour period nothing was allowed by mouth (Part I). A 5% solution of dextrose in water was given intravenously to replace fluid loss. Early in these studies the amount of dextrose given was 4,000 cc. This was later decreased to 3,000 cc. No saline was given.

All materials from gastric aspiration and urine secretion were collected and measured. A sample of each was sent to the laboratory for chloride determination. This analysis was done by the usual Van Slyke method and reported in terms of chloride expressed as sodium chloride.

Part II followed Part I and was identical except that during the 24-hour gastric aspiration the patient was given 4,000 cc. of water by mouth. This was decreased to 3,000 cc. during the latter half of these investigations. This decrease did not seem to alter the results and was accompanied by fewer complaints on the part of the patient.

Occasionally, Part II preceded Part I in order to determine whether this caused any variation in the chloride values. It made none that could be determined. Early in this study the two parts followed each other on consecutive days. This often was quite trying to our subjects. Therefore, during the latter half of the series, one day of grace with food was allowed between the two test days. This variation also caused no noticeable difference.

Tests were run on 50 patients. Of these, four were omitted from analysis because of errors in collecting and reporting. This leaves the tests of 46 patients upon which to base our results. Of these 46, all presented peptic ulcer problems except for 13. These 13 "normals" were a mixed groups of patients with hernia, appendicitis, and peripheral vascular disease.

At the onset of this study it was hoped that blood and plasma values might also be correlated with gastric losses brought about by aspiration. As is well known, such blood changes are zealously guarded by the physiological processes of the body and occur only as late evidence of a failing balance. Because of the definite risk involved, no tests were carried to these extremes. Blood chloride and CO_2 determinations taken during the tests were normal with one exception.

Chloride was used as the electrolyte for analysis because it is representative, important, and easily titrated. Determinations of other electrolytes were not done, and by inference it is assumed that their loss from the stomach would parallel that of the chloride. This is certainly true for potassium loss by aspiration.[4]

RESULTS

A graphic résumé of the tests run on our 46 patients is indicated in Charts 1 and 2. Here it is shown that the average amount of gastric fluid aspirated from

3. Drs. P. W. Steele, R. M. Raber, A. R. Madtson, T. L. Dittmer, E. H. Winterhoff, and D. O. Porter.

4. Lans, H. S.; Stein, I. F., and Meyer, K. A.: Diagnosis, Treatment and Prophylaxis of Potassium Deficiency in Surgical Patients: Analysis of 404 Cases, Surg., Gynec. & Obst. **95**:321, 1952.

Part I patients in the 24-hour test period was 1.83 liters. That aspirated during Part II, when the patient was required to drink three liters of tap water besides that received by vein, averaged 5.15 liters.

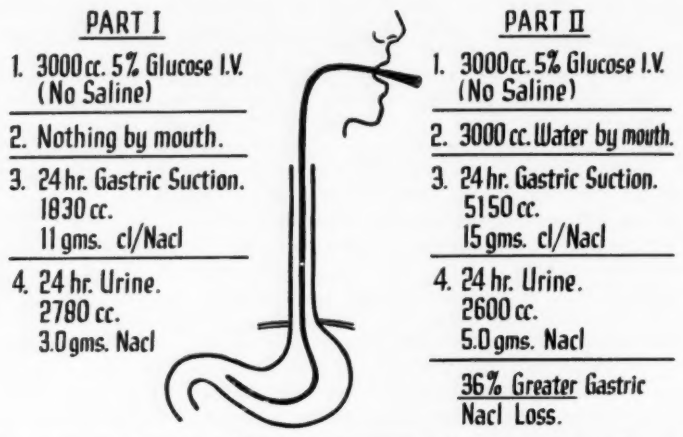
PART I
1. 3000 cc. 5% Glucose I.V. (No Saline)
2. Nothing by mouth.
3. 24 hr. Gastric Suction. 1830 cc. 11 gms. cl/Nacl
4. 24 hr. Urine. 2780 cc. 3.0 gms. Nacl
PART II
1. 3000 cc. 5% Glucose I.V. (No Saline)
2. 3000 cc. Water by mouth.
3. 24 hr. Gastric Suction. 5150 cc. 15 gms. cl/Nacl
4. 24 hr. Urine. 2600 cc. 5.0 gms. Nacl
36% Greater Gastric Nacl Loss.

Chart 1.—Amount of gastric fluid and chloride removed by the average nasal-gastric suction tube in a 24-hour period. The chloride is transposed to terms of sodium chloride. In Part I, nothing was given by mouth. Part II differs in that 3,000 cc. of water was given by mouth. It will be noted that the chloride loss is 36% greater when this amount of water by mouth is allowed.

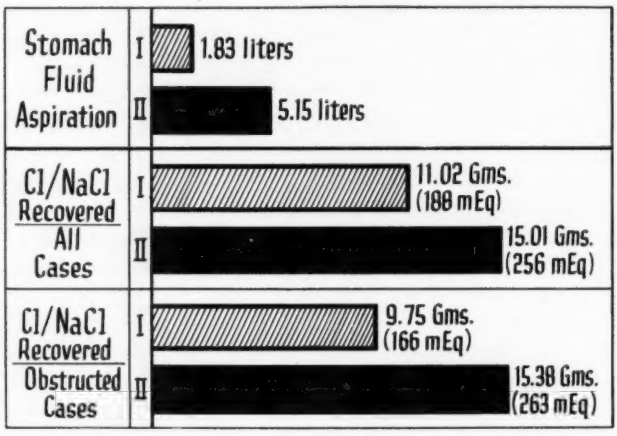

Chart 2.—Shaded columns, Part I; black columns, Part II, water by mouth. Condensed results indicate that the average aspiration by nasal-gastric suction tube amounts to 1.83 liters, while water ad libitum increases this to 5.15 liters. Average chloride loss (expressed in terms of NaCl) for all cases studied, was 36% greater (Part II) when water was allowed by mouth. A 57% greater loss in Part II was noted in 25 patients who had some degree of pyloric obstruction.

It should be emphasized that these results are averages, and that the individual findings varied a great deal. This variation was in part due to the fact that the aspiration tubes were not uniformly placed in the stomach. Had the tubes been

placed in the stomach under fluoroscopic vision, as suggested by others,[5] the amounts of fluid and electrolyte withdrawn would have been more uniform. However, the random placing of the tubes in this study has the virtue of representing a cross section of the average postoperative gastric suction. It gives the usual amount withdrawn, not the maximum which might be removed with the tube end optimally placed in the stomach under fluoroscopic control.

In Part I, with no water by mouth, an average 188 mEq. of chloride was aspirated. This expressed as sodium chloride is equal to 11.02 gm. lost in a 24-hour period. During the same length of time, in the same patients undergoing Part II. with water by mouth, 256 mEq. was lost. This expressed as sodium chloride averages 14.01 gm. and is an increased loss of 36% over that in Part I. This increased chloride loss will be discussed later.

A slight error occurred in some patients undergoing Part II. In a few, a considerable amount of swallowed water passed through the pylorus before it was aspirated by the gastric suction tube. This "error" occurred to a lesser extent in those patients with gastric retention. It was of interest to consider separately those patients who had some degree of gastric retention. All patients were therefore arbitrarily catalogued as to their degree of obstruction—0, 1, 2, and 3 +. Complete obstruction was indicated by 3 +, and there was only one such case in this series. There were 25 patients who were considered to have a 2+ degree of obstruction.

An obstructive factor at the pylorus is considered by many to lead to an excessive chloride loss.[6] This was not altogether confirmed in the present study, for if these patients with obstruction were given no water by mouth they lost no more chloride than the general average (166 mEq. or 9.75 gm. of sodium chloride per 24 hours). However, as compared with the loss in Part II (263 mEq or 15.38 gm.) this difference was appreciable. The increase in chloride lost by aspiration in a patient taking water ad libitum thus amounted to 57.5% over those deprived of water by mouth. This figure, then, bears considerable meaning. It indicates that the common practice of allowing patients with indwelling gastric tubes to drink water as they wish may add a burden which the sick postoperative patient can ill afford. An added electrolyte loss of 50% over that usually removed by gastric suction cannot be considered lightly.

The amounts of urine passed in the 24-hour period and its chloride content were determined for each of the 46 patients. The results were not remarkable. At times the amount of urine in Part II was considerably more than that in Part I. This was interpreted as indicating that much of the swallowed water of Part II passed through the pylorus into the intestine, to be picked up by the blood stream and kidneys.

5. Farmer, D. A.; Howe, C. W.; Porell, W. J., and Smithwick, R. H.: The Effect of Various Surgical Procedures upon the Acidity of the Gastric Contents of Ulcer Patients, Ann. Surg. **134**:319, 1951.

6. Clarke, J. S.; Oberhelman, H. A.; Evans, S. O., and Dragstedt, L. R.: The Relation of Gastric Secretion to Events Following Pyloric Obstruction, Ann. Surg. **135**:433, 1952. Lans, H. S.; Stein, I. F., and Meyer, K. A.: Electrolyte Abnormalities in Pyloric Obstruction Resulting from Peptic Ulcer or Gastric Carcinoma, Ann. Surg. **135**:441, 1952. Sanchez-Vegas, J., and Collins, E. N.: Importance of Urinary Chloride Determinations in Treatment of Patients Having Pyloric Obstruction: Review of 50 Cases of Duodenal Ulcer, Am. J. M. Sc. **211**:428, 1946.

rather than through the gastric suction tube. The average amount of 24-hour sodium chloride excreted in the urine of Part I was 3 gm., while that of Part II was 5 gm.

COMMENT

The nasal-gastric suction tube is such a useful and important tool that we must continually warn ourselves of its dangers. It may remove electrolytes just as surely and completely as does a violent emesis, yet it does so stealthily and without warning. The violent vomiting sounds its own alarm, while the suction tube muffles and obscures these early signals.

This study indicates the very large amounts of electrolyte and fluid which may be removed through the usual gastric suction tube. The figures are somewhat higher than those previously presented.[7] They reemphasize the rapidity with which the

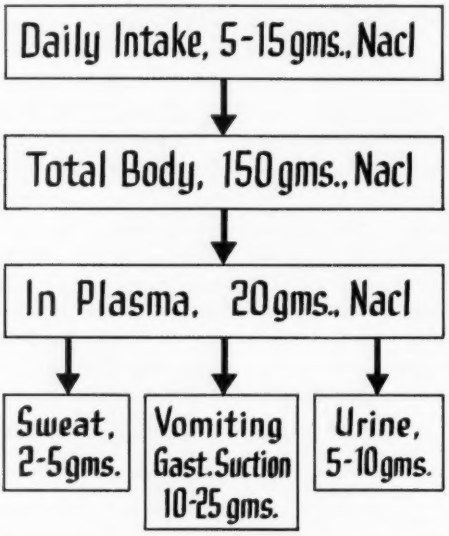
Daily Intake, 5-15 gms., Nacl
Total Body, 150 gms., Nacl
In Plasma, 20 gms., Nacl
Sweat, 2-5 gms.
Vomiting Gast. Suction 10-25 gms.
Urine, 5-10 gms.

Chart 3.—Diagram indicates roughly the large amounts of total chloride (expressed as NaCl) which may be lost by gastric suction or by vomiting.

body may lose its electrolytes by aspiration (Chart 3). Oral replacement allows for an automatic balance, but this of course is eliminated with the use of the tube. The patient becomes entirely dependent upon the surgeon's judgment as to fluid needs. Therefore, careful estimation of loss and parenteral replacement is the only alternative. There need be no further discussion of the dangers of gastric aspiration. Consideration of what is commonly removed daily should be warning enough.

The average amounts of fluid and electrolyte lost in these numerous tests were large. They do not, however, represent the maximal amounts which might be lost if the tube had been placed in the stomach under fluoroscopic vision. From this standpoint the foregoing account falls short of being physiologically accurate. Nevertheless, it is clinically accurate in that it presents the results of the clinically inserted gastric tube in the average case.

7. Van Slyke and Evans.[1a] Bartlett and others.[1b] Abbott.[1d]

As indicated, there is an undeniable increase in electrolyte loss in the gastric suction patient who is allowed water by mouth. Practice has shown this increased loss to be unimportant in the usual patient when gastric aspiration is not extended beyond a three-day period. However, in critical situations with suction continuing over many days this excess loss becomes quite important and must be replaced. A far better procedure would be not to let it occur in the first place and to satisfy the patient's thirst and prevent dehydration by intravenous fluids.

One of the patients making up this series illustrates the ease with which a patient may be thrown into serious alkalosis by the mere aspiration of gastric contents. This is the only case in which such a complication arose. Because of its lesson, it is detailed briefly as follows:

A. J., No. 54133, was a well-nourished 51-year-old man with a 25-year history of duodenal ulcer and of bleeding in 1947 and 1949. He was admitted to the Veterans Administration Hospital in October, 1951, with epigastric pain and vomiting. Ulcer dietary management, antacids, and methantheline (banthine®) had failed, and the patient was transferred to the Surgical Service for gastric resection. Chloride tests were initiated prior to surgery to better evaluate the patient's problem. Just 11 hours after Part I was started with simple gastric suction and intravenous dextrose, the patient suddenly felt cold, had tingling of lips and hands, and hyperactive reflexes. Blood pressure dropped to 100/50 from a normal 160/95. Alkalosis was immediately suspected and was confirmed by laboratory findings of 45 mEq. of CO_2 and 82 mEq. of serum chloride. Intravenous administration of fluids, calcium gluconate, and sodium chloride resulted in clinical improvement with CO_2 fall to 38 mEq. and serum chloride rise to 97 mEq. A week later the patient completed both parts of the chloride test. At the termination of Part II he was again in moderate alkalosis and tetany. This condition responded as before to saline and calcium gluconate. He was operated upon later without incident.

This case illustrates two very important points. First of all, the patient was in subclinical alkalosis from his antacid therapy before he was admitted to the hospital. Had he been operated upon immediately, he most certainly would have gone into an unsuspected postoperative alkalosis. Second, the added chloride loss caused by tap-water washings of the gastric mucosa might have been a sufficient added burden to prevent compensation or at least to make its achievement very difficult.

SUMMARY AND CONCLUSIONS

The nasal suction tube may become quite a dangerous postoperative tool in that it removes large quantities of gastric electrolyte. This is done insidiously without the drama and demand for action accompanying active emesis.

An analysis was made of the amount of chloride removed by means of the nasal gastric suction tube from 46 hospital patients. Over a 24-hour period this chloride loss averaged 188 mEq. (11.02 gm. expressed as sodium chloride). During the same period an average of 1.93 liters of fluid was aspirated from the inactive stomach.

The practice of allowing patients with gastric suction to take water ad libitum causes an increased amount of chloride to be washed from the gastric mucosa. The increased loss was found under varying conditions to be a third to a half greater than when no water was allowed orally. This additional loss is of no consequence when the gastric suction is applied for only two or three days. But in more complicated situations it may become the deciding factor in survival.

Postoperative patients may be kept perfectly comfortable, and thirst can be avoided by proper intravenous fluids alone.

DISCUSSION

DR. G. W. NAGEL, San Francisco: One thing has not been suggested in this paper, and I am very much interested in it.

Why use suction? That is what we are doing now, in the average case. The essayist's figures convince me that we are right about that. I was brought up, of course, without an opportunity to use suction at all. W. J. Mayo's remark may be considered trite, but it was very fundamental at the time. He used to say that he would rather see his resident with a stomach tube in his pocket than a stethoscope.

We didn't have suction in the earlier days. I would hate to admit it was so long ago that I was trained. The average postoperative patient got along fine. We started feeding these patients quite soon, and they had no difficulty at all. Occasionally, of course, one had to be on the qui vive, and when necessary a stomach tube was used.

Now we have gone back to the old method. We haven't quite had the courage to leave the tube out completely in resections. We put it in, but we don't apply suction; we just let the tube drain for 12 or 24 hours and then take it out. I am sure our patients do much better.

I think the proof of it is that our resident staff is quite convinced of that fact.

DR. WILLARD BARTLETT, St. Louis: We should welcome heartily Dr. Taylor's presentation, which sets forth additional evidence bearing on an important detail of the suction regimen. In my own publications since 1931 elaborating the concept of pyloric balance, I have insisted that, except in unusual instances, (1) suction should be gastric, not duodenal, and (2) oral intake or irrigating fluid should be kept to a minimum of 30 cc. per hour during the waking hours.

In support of the latter point I have urged the view, based on experimental evidence, that increase in the fluid content of the distended stomach and small bowel accelerates the rate at which they secrete water and electrolytes. The provision of a large oral intake or of copious irrigation not only intensifies the process which one seeks to minimize by continuous suction decompression, but also effects lavage with a hypotonic solution whose ability to reduce the serum concentration of sodium, chloride, and potassium has therapeutic merit in other applications.

To revert to Dr. Taylor's study of the "average" use of the tube, the soundness of the views which I have propounded is shown by the fact that to adult patients in whom suction is started postoperatively in the absence of electrolyte deficit, neither saline solution nor potassium is ordinarily given during the suction regimen. Why?

Because, in the absence of mechanical intestinal or pyloric obstruction, the volume of gastrointestinal secretions lost by suction will not exceed 1 liter per 24 hours and, in the absence of peritonitis, will rarely exceed 500 cc. per day. The losses of sodium, chloride, and potassium in such a volume of fluid over a period of only two or three days are trifling. The loss of potassium in the urine is inconsequential during such a period if only dextrose or invert sugar is given parenterally and if sodium chloride is withheld. I wish it to be emphatically clear that I am excluding the patient who has deficits to start with.

I have not withheld all oral intake from the patient on a suction regimen. The small volume of 30 cc. per hour when awake not only improves oral hygiene and morale, but enables the patient and attendants to watch the advance of fluid in the suction apparatus to make certain that effective suction is being provided.

Finally, if only small, rather than large, quantities of ingested fluids or irrigating solutions are employed, the occasional inevitable errors in recording of volumes are minimized in importance when one comes to calculate the pyloric balance which is arrived at by comparison of the 24-hour oral intake with the volume of material aspirated during that period.

NEW ANTIHEPARIN AGENT ("POLYBRENE")

Effect in Peptone Shock and in Experimental Radiation Injury

FREDERICK W. PRESTON, M.D.
AND
ROBERT P. PARKER, M.D.
CHICAGO

OUR INTEREST in antiheparin agents was stimulated by recent reports of Allen and associates [1] that the hemorrhagic syndrome which follows total body exposure to ionizing radiation is caused by a circulating anticoagulant. Not only have physicians been called upon to treat large numbers of casualties exposed to lethal radiation from atomic weapons in warfare, but, as the atomic energy industry has expanded, accidental exposure of human beings to lethal doses of radiation has occurred.[2] Under these circumstances drugs to correct the coagulation defect of radiation injury might be most useful. Allen and associates were able to neutralize the hypocoagulability of blood in experimentally irradiated dogs by the intravenous injection of protamine sulfate and toluidine blue. These investigators also found that the coagulation time of normal plasma was prolonged by the addition of irradiated dogs' blood. These findings led to the conclusion that the circulating anticoagulant was endogenous heparin.[1]

The purpose of this paper is to show the effect of a potent antiheparin agent ("polybrene") on the hemorrhagic defect of radiation syndrome and on the coagulation defect of peptone shock.

"Polybrene" [3] is a quaternary ammonium salt having an empirical formula as follows: $(C_{13}H_{30}Br_2N_2)x$. It is a polymer, probably linear, of N, N, N′, N′-tetramethylhexamethylenediamine and trimethylene bromide.[4] Its structural formula and chemical name are given in the Figure. It is similar to protamine sulfate and toluidine blue in that it neutralizes heparin in vivo and in vitro and is itself an anti-

Mr. Merle Fitz gave technical help during the completion of this work.

From the Department of Surgery, Northwestern University Medical School.

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1. (*a*) Allen, J. G., and Jacobson, L. O.: Hyperheparinemia: Cause of the Hemorrhagic Syndrome Associated with Total Body Exposure to Ionizing Radiation, Science **105**:388-389, 1947. (*b*) Allen, J. G.; Sanderson, M.; Milham, M.; Kirschon, A., and Jacobson, L. O.: Heparinemia(?). An Anticoagulant in the Blood of Dogs with Hemorrhagic Tendency After Total Body Exposure to Roentgen Rays, J. Exper. Med. **87**:71-86, 1948.

2. Hempelmann, L. H.; Lisco, H., and Hoffman, J. G.: The Acute Radiation Syndrome: Nine Cases and a Review of the Problem, Ann. Int. Med. **36**:279-510, 1952.

3. Supplied by the Abbott Laboratories.

4. Moore, M. B.: Personal communication to the authors.

coagulant both in vivo and in vitro. We have found that approximately 7.5 mg. of "polybrene" neutralizes the in vivo anticoagulant effect of 10 mg. of heparin (1000 units U. S. P.).[3]

Peptone shock in the dog is a condition which has been studied intensively, particularly by physiologists interested in the coagulation defect and the circulatory collapse which are characteristic of this condition. It has been demonstrated that the hypocoagulability of blood in peptone shock is caused by endogenous heparin, the source of which is the shocked animal's liver.[5]

The effectiveness of "polybrene" in neutralizing this coagulation defect is in marked contrast to its failure to neutralize the coagulation defect in radiation syndrome.

EXPERIMENTS

In Vivo Studies

Peptone shock was produced in seven mongrel dogs weighing from 7 to 10 kg. by the intravenous injection of 10 to 20 cc. of 10% "bacto-protone"[6] solution. All dogs except one were anesthetized with pentobarbital sodium. Control coagulation times of these animals immediately before the injection of "bacto-protone" varied from 10 to 15 minutes, as measured by a three-tube Lee and White method.[7] Within three minutes after injection there was a precipitous fall in blood pressure to shock levels, the systolic fall averaging 90 mm. of mercury for the seven animals. Coincident with the drop in pressure there was prolongation in the blood coagulation time to 56 minutes or more. "Polybrene" in doses of 0.9 to 2.2 mg. per kg. restored the coagulation time approximately to control levels within a few minutes after injection in six animals, and in the seventh (Dog 17) there was a decrease in coagulation time from over an hour to 32 minutes (Table 1).

To determine the effect of "polybrene" on the coagulation defect of radiation syndrome, 13 dewormed dogs weighing from 6 to 10 kg. were exposed to 350 to 400 r total body x-irradiation.[8] Marked depletion of thrombocytes and leucocytes, purpura of the skin and oral mucous membranes, bleeding into internal organs, and ultimately death occurred in all animals. Definite prolongation of the coagulation time, varying from 22 to 100 minutes, was apparent 8 to 17 days after exposure. During the period of study of these animals (from the 8th to the 18th

5. (*a*) Quick, A. J.: On the Coagulation Defect in Peptone Shock: Consideration of Antithrombins, Am. J. Physiol. **116**:535-542, 1936. (*b*) Wilander, O.: Studien über Heparin, Skandinav. Arch. Physiol., Supp. 15, p. 81, 1938. (*c*) Waters, E. T.; Markowitz, J., and Jaques, L. B.: Anaphylaxis in the Liverless Dog, and Observations on the Anticoagulant of Anaphylactic Shock, Science **87**:582-583, 1938.

6. Manufactured by Difco Laboratories, Detroit.

7. One cubic centimeter of blood was drawn by clear jugular venipuncture with use of a No. 21 needle 1¼ in. (3 cm.) in length. The syringe was then discarded and a siliconized 10-cc. syringe was attached and 3 cc. of blood was withdrawn. One cubic centimeter of blood was placed in each of three clean, dry nonsiliconized tubes measuring 1 cm. (inside diameter) by 8 cm. (length). Five minutes after the blood was placed in the tube each tube was tilted at one-minute intervals until coagulation occurred, as evidenced by failure of the blood to flow upon complete inversion of the tube. The coagulation time was determined as the time elapsed between placement of the blood in the tubes and coagulation of the blood in all the tubes. All determinations were made by one author (F. W. P.) and one technician. The coagulation time for normal unanesthetized dogs by this method varied from 8 to 12 minutes.

8. Physical factors were 220 Kv., 20 ma., 0.5 mm. Cu + 1 mm. Al. filtration. The target skin distance was 150 cm. With these factors, the r per minute in air was calculated at 4.22. This was verified by ionization chamber measurements in air at the center and at the periphery of a 20-in. (50-cm.) diameter field. The "fall off" from the center to the periphery was found to be less than 10%. Dogs were irradiated with the entire body within the 20-in. diameter field, receiving half of the total exposure on each side.

TABLE 1.—*Effect of "Polybrene" on Coagulation Defect of Peptone Shock* *

Dog	Coag. Time Before Onset of Shock, Min.	Coag. Time During Peptone Shock, Min.	Dose "Polybrene," Mg./Kg.	Interval After "Polybrene" Injection, Min.† 0-10 Coagulation Time, Min.	11-30 Coagulation Time, Min.	31 or Over Coagulation Time, Min.
14	12	56	1	.....	12 (17 min.)	.....
15	10	> 60	1	12 (6 min.)	.....	8 (38 min.)
16	15	> 60	2.2	18 (immediately post mortem)	.....	.....
17	14	> 60	2	60 (2.5 min.)	32 (18 min.)	20 (32 min.)
18	11	>150	1.5	9 (10 min.)	10 (24 min.)	10 (34 min.)
19	12	>150	0.9	10 (1.5 min.) 9 (3.5 min.)	11 (14 min.)	.....
20	12	>150	1.4	10 (10 min.)	.....	.....

* Shock was produced in Dog 14 without anesthesia. The other dogs were anesthetized with pentobarbital sodium before injection of "bacto-protone."

† Exact time intervals are given in parentheses.

TABLE 2.—*Effect of "Polybrene" on Blood Coagulation Time Following Total Body X-Irradiation* *

Dog	Day After X-Irradiation	Coag. Time, Min.	Dose "Polybrene," Mg./Kg.	Interval After "Polybrene" Injection, Min.† 5-10 Coagulation Time, Min.	11-30 Coagulation Time, Min.	31-120 Coagulation Time, Min.	More Than 120 Coagulation Time, Min.
1.....	10	76	1	48	...	.....	.....
	10	80	1	92	150	.....	.....
2.....	16	42	1.5	..	...	56 (68 min.)	100 (22 hr.)
				..	...	90 (90 min.)	.....
	17	100	1	..	...	40 (70 min.)	42 (23 hr.)
				..	...	60 (90 min.)	30 (31 hr.)
3.....	12	42	1.3	..	42	.....	25 (5.5 hr.)
4.....	12	16	1.5	13	...	.....	.....
	14	43	1.5	19	...	.....	.....
	15	22	1.5	..	24	.....	.....
5.....	11	60	2	37	25	.....	.....
6.....	8	27	2	26	...	.....	21 (6 hr.)
	9	38	2	43	36	.....	.....
7.....	9	28	2.2	44	...	.....	.....
8.....	11	45	1.4	55	60	85 (75 min.)	.....
9.....	11	35	1.1	45	40	40 (120 min.)	.....
10.....	10	60	1.3	..	57	119 (34 min.)	.....
	10	43	2.7	180	90	.....	.....
11.....	10	62	1.3	48	...	.....	102 (3 hr.)
				..	...	.....	60 (5 hr.)
	10	60	1.1	75	70	.....	.....
12.....	10	26	3.3	..	34 (13)	47 (33 min.)	.....
				..	39 (23)	.....	.....
13.....	10	36	1.9	..	...	80 (50 min.)	16 (5 hr.)

* Control coagulation times before irradiation varied from 8 to 10 min. Dogs 1 and 2 received 350 r total body x-irradiation; the remaining dogs received 400 r.

† Exact time intervals are given in parentheses.

postradiation day) penicillin was administered intramuscularly in an effort to prolong life by combating infection. No other medication was given. Immediately after a prolonged coagulation time was obtained 1 to 3.3 mg. per kilogram of "polybrene" was injected, and coagulation time determinations were made thereafter at intervals for the following 24 hours (Table 2). In no case did lowering of the coagulation time to control levels (8 to 10 minutes) occur, and in general "polybrene" seemed to have no effect on the blood coagulation time of irradiated animals.

In Vitro Studies

Like the protamines, "polybrene" has an inhibitory effect on the clotting of blood in vitro, and it is possible to titrate for unknown quantities of heparin by means of known concentrations of "polybrene." This property of protamine is the basis for the titration studies made by Chargaff and Olsen [9] and by Jaques and associates,[5c] and is the basis for the titration tests for circulating heparin described by Allen and associates [11] and by LeRoy, Halpern, and Dolkart.[12] The shortest clotting time in a series of test tubes containing normal whole blood occurs in the tube in which the amount of protamine and heparin exactly neutralize each other. If either occurs in excess the clotting time is prolonged.

Table 3.—*Effect of "Polybrene" on Normal Dogs' Blood Before and After Intravenous Injection of Heparin and During Peptone Shock (in Vitro Titrations)*

"Polybrene" Mg. in 0.1 Cc. Saline Solution	Coagulation Time 0.5 Cc. Blood, Min.			
	Normal Dog		Dog 14	
	Control	After Heparin Sodium, 1 Mg./Kg.	Control	During Peptone Shock
0.000	8	28	7	36
0.001	10	14	9	19
0.004	11	14	14	13
0.008	15	14	19	19
0.012	15	17	21	24
0.016	23	21	33	43
0.020	27	33	58	>45
0.024	28	39	66	>45

Into each of eight test tubes measuring 1 cm. (inside diameter) by 8 cm. (length) was placed 0.1 cc. of isotonic sodium chloride solution containing varying amounts of "polybrene," as indicated in Tables 3 and 4. Immediately after withdrawal from a jugular vein 0.5 cc. of dogs' blood was pipetted into each tube. The tubes were rapidly inverted 8 to 10 times to thoroughly mix the contents and tilted at 1 minute intervals thereafter until clotting occurred.

In samples of blood from 11 normal dogs clotting occurred first in the tube containing saline only and was delayed in the other tubes in proportion to the amount of "polybrene" present. Frequently no coagulation had occurred in tubes containing 0.02 mg. or more at the end of 60 minutes.

9. Chargaff, E., and Olsen, K. B.: Studies on the Action of Heparin and Other Anticoagulants: The Influence of Protamine on the Anticoagulant Effect in Vitro, J. Biol. Chem. **122**:153-167, 1938.

10. Footnote deleted.

11. Allen, J. G.; Moulder, P. V.; Elgehammer, R. M.; Grossman, B. J.; McKeen, C. L.; Sanderson, M.; Egner, W., and Crosbie, J. M.: A Protamine Titration as an Indication of a Clotting Defect in Certain Hemorrhagic States, J. Lab. & Clin. Med. **34**:473-476, 1949.

12. LeRoy, G. V.; Halpern, B., and Dolkart, R. E.: An Indirect Quantitative Method for the Estimation of Heparin Activity in Vitro: The Heparin-Protamine Titration Test, J. Lab. & Clin. Med. **35**:446-458, 1950.

Approximately five minutes after the injection of heparin in doses of 1 to 1.5 mg. per kilogram into six normal dogs, blood was withdrawn and 0.5 cc. placed in each of eight tubes. An in vitro neutralization was apparent as evidenced by faster coagulation in a "polybrene"-containing tube than in the tube containing saline only (Table 3).

Titrations were done on the blood of six dogs before and during peptone shock. A typical result is shown in Table 3 (Dog 14). All the titrations were negative for heparin before the onset of shock and were positive for heparin during shock.

Samples of blood from seven dogs with radiation syndrome whose whole blood coagulation times were greater than 17 minutes were used to titrate against "polybrene." The blood of six animals clotted in the saline tube first and thereafter in the other tubes in proportion to the concentration of "polybrene," as indicated in Table 4.

The blood of one irradiated dog (Dog 5) on three different occasions during a 24-hour period clotted in several "polybrene"-containing tubes before it clotted in the saline control. It is interesting that in this animal there was a drop in the whole blood clotting time from 60 minutes to 37 minutes when "polybrene" was injected intravenously (Table 2). These findings suggest an increase in the concentration of heparin in the blood of this animal.

TABLE 4.—*Effect of "Polybrene" on Blood of Dogs Exposed to Total Body X-Irradiation (in Vitro Titrations)*

Dog	1	3	12	13	14	15	5
Day after irradiation	7	14	10	13	9	8	11
Whole blood clotting time (min.)	18	42	26	24	47	37	37
Mg. "Polybrene" in 0.1 Cc. Saline Solution	Clotting Time 0.5 Cc. Blood, Min.						
0.000	14	19	17	12	21	23	17
0.001	15	44	18	45	30	23	17
0.004	18	120	23	45	180	41	17
0.008	30	>120	25	>45	>180	73	12
0.012	30	>120	34	>45	>180	101	15
0.016	50	>120	39	>45	>180	>120	16
0.020	50	>120	82	>45	>180	>120	21
0.024	..	>120	90	..	>180	>120	22

Several attempts were made in other animals with radiation syndrome to titrate for the presence of a heparin-like anticoagulant with "polybrene," but the results were considered equivocal because of the failure of clotting to take place in the system of tubes in any consistent sequence. It is unlikely that these equivocal tests were solely the result of errors in technique because similarly unsatisfactory titrations were encountered much less frequently in samples of blood from normal and heparinized dogs and from dogs in peptone shock. It is probable that this method of study of the coagulation defect is difficult to apply to irradiated dogs' blood because of failure to control other coagulation factors.

COMMENT

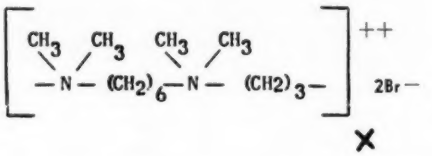
In the present study attempts to restore normal clotting time to the blood of dogs with the hemorrhagic defect of experimental radiation syndrome are reported. A new stable antiheparin agent, "polybrene," was used in titration studies and as an in vivo heparin inhibitor. Its effect in radiation syndrome was compared to its effect on the coagulation defect of peptone shock, a condition known to be caused by endogenous heparin.

The coagulation defect of peptone shock is identical with that produced by the intravenous injection of commercial heparin. Prolonged blood clotting times of both

conditions can be restored to normal within a few minutes after intravenous injection of appropriate amounts of "polybrene." In dogs with radiation syndrome no definite alterations of prolonged coagulation times were noticed in most cases after "polybrene" administration.

Since "polybrene" is itself an anticoagulant, it can be used in an in vitro titration to detect the presence of heparin in blood. By such a method heparin was consistently detected in the blood of dogs in peptone shock and in dogs which had received injections of 1 mg. of heparin per kilogram (100 units U. S. P.). Although some titrations run on irradiated dogs' blood were equivocal and one irradiated dog had a titration consistently positive for heparin, in most animals no circulating heparin or heparin-like substance could be detected.

Jackson, Cronkite, LeRoy, and Halpern [13] state that the two principal changes in the clotting elements which occur in radiation syndrome are decrease in thrombocytes and increase in blood fibrinogen, and that the former finding accounts for the coagulation defect. Our results substantiate the conclusions of these authors and of Holden and associates [14] that a circulating anticoagulant which can be neutralized by antiheparin agents is usually not present in dogs with radiation syndrome.



"Polybrene" (1,5-dimethyl-1,5-diazaundecamethylene polymethobromide).

SUMMARY AND CONCLUSIONS

"Polybrene," a polymer of N, N, N′, N′-tetramethylhexamethylenediamine and trimethylene bromide, neutralizes the anticoagulant action of heparin in vivo and in vitro and is itself an anticoagulant.

Intravenous "polybrene" rapidly neutralized the hypocoagulability of blood following the injection of commercial heparin and the hypocoagulability of peptone shock but had no effect on the coagulation defect of radiation syndrome.

By means of a titration using "polybrene," circulating heparin was detected after the injection of commercial heparin and in dogs in peptone shock. No heparin could be detected in normal dogs' blood or in dogs with radiation syndrome.

Evidence is presented which indicates that circulating heparin is usually not present in untreated experimental radiation syndrome.

13. Jackson, D. P.; Cronkite, E. P.; LeRoy, G. V., and Halpern, B.: Further Studies on the Nature of the Hemorrhagic State in Radiation Injury, J. Lab. & Clin. Med. **39**:449-461, 1952.

14. Holden, W. D.; Cole, J. W.; Portmann, A. F., and Storaasli, J. P.: Hypothromboplastinemia Following Total Body Irradiation, Proc. Soc. Exper. Biol. & Med. **70**:553-556, 1949.

DISCUSSION

DR. JOHN OLWIN, Chicago: I should like to compliment Dr. Preston on his work with this new drug, and on his demonstration that it will effectively neutralize heparin both in vitro and in vivo. I should like to emphasize certain points that he made about the effect of antiheparin drugs in radiation syndrome.

As many of you know, the original work on the bleeding tendency in radiation syndrome was done by Dr. Garrett Allen at the University of Chicago shortly after the war. He found that in addition to the depression of thrombocytes there was a hyperheparinoid state that could be neutralized by the antiheparin drug protamine or by certain of the dyes, particularly toluidine blue, which was the least toxic of those dyes, and that thereby the hemorrhagic tendency was materially reduced, although not entirely neutralized.

Later, when he tried to repeat this work, the heparinoid state did not develop. When he reviewed his original work he discovered that the animals of that study had in nearly every instance received whole blood transfusions. Those that received the most blood, for the most part, had the more severe hyperheparinemia. He then retracted his original thesis, namely, that irradiation produced the heparinoid state, and he concluded that it was primarily an anaphylactoid reaction to the blood, aggravated but not produced by gamma rays.

He further showed that this may happen to patients at the time of surgery, as an anaphylactoid reaction to blood, sometimes as a result of improper matching. The oozing state thus produced could be shown to be on the basis of a hyperheparinoid state, and titration with antiheparin drugs would reveal this; it could be neutralized at the operating table if antiheparin drugs were given

This work is reported in the Transactions of the Fifth Conference on Blood Clotting and Allied Problems, under the Josiah Macy, Jr., Foundation, New York, which are not yet in print. It explains Dr. Preston's findings that "polybrene" does not neutralize the bleeding tendency in radiation syndrome, which, as he stated, is now believed to be primarily on the basis of thrombocytopenia and generalized tissue damage.

INTRAVENOUS TRYPSIN IN THE TREATMENT OF THROMBOTIC PHENOMENA

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AND
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CHICAGO

THE FIBRINOLYTIC properties of trypsin have been known for some time. Recently, Innerfield and his associates [1] reported that under certain conditions of administration and dosage the enzyme could be given intravenously to animals and to patients without untoward effects. These workers stated that the intravenous administration of trypsin caused the dissolution of thrombi and also caused a remarkable subsidence of a variety of acute inflammatory conditions. For many years investigators interested in the the thrombosis problem have sought a nontoxic in vivo thrombolytic agent. Therefore the claims of Innerfield's group warrant serious investigation.

We wish to report our clinical experiences with 30 cases of acute and chronic peripheral thrombotic disease and to summarize some preliminary data from our animal studies.

CLINICAL EXPERIENCES

Dose.—Innerfield and his group recommended a dose of 100,000 to 250,000 units of crystalline trypsin [2] diluted in 250 cc. of saline once or twice a day. They had given up to 750,000 units a day over a four-day period to one patient and noticed minor purpuric phenomena in this patient. They recommended that infusions be given in rates between 25 to 30 drops a minute, since they thought that rates faster than these might conceivably initiate a shock-like state.

With this plan of administration we noted that in practically every patient local pain, tenderness, and redness at the site of infusion developed. The reasons for this discomforting reaction are not altogether known, but we have assumed that it may be due to the fact that in proper small concentrations trypsin will convert prothrombin to thrombin, or it may be the result of the low pH of the saline solution of trypsin. Consultation with other investigators of this problem resulted in the suggestion that certain changes in administration be substituted.

In the most recently treated patients, we have largely done away with severe local reactions by the following combination of measures: (1) administration of

From the Department of Surgery, Northwestern University Medical School.

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1. Innerfield, I.; Schwartz, A. W., and Angrist, A. A.: Fibrinolytic and Anticoagulant Effects of Intravenous Crystalline Trypsin, Bull. New York Acad. Med. **28**:537, 1952.

2. Enzar, developed, manufactured and supplied by the Armour Laboratories, Chicago, consists of 90% pure trypsin; 5% ash (mostly magnesium); 4% traces ribonuclease plus cathepsin and alpha, beta, and gamma chymotrypsin; 1% undetermined.

250,000 units of trypsin dissolved in 500 cc. isotonic sodium chloride solution; (2) infusion made at the rate of 1 drop a second; (3) use of a No. 23 gauge needle, and (4) elevation of the arm to promote rapid venous flow past the point of infusion.

Other investigators [3] have been using somewhat smaller doses ranging from 50,000 units twice daily to 100,000 units twice daily dissolved in 100 cc. of isotonic sodium chloride. Such doses are not, as a rule, accompanied by local reactions.

Acute Thrombophlebitis.—Within our small group of 10 cases of acute thrombophlebitis we found that there was a great variation in the type of disease with regard to (1) the age of the lesion before treatment, (2) the location and extent of involvement by objective examination, (3) the degree of febrile response, and (4) the degree of subjective pain.

To illustrate the nature of these cases we wish to present a short summary of samples from this group. Laboratory data will be summarized separately.

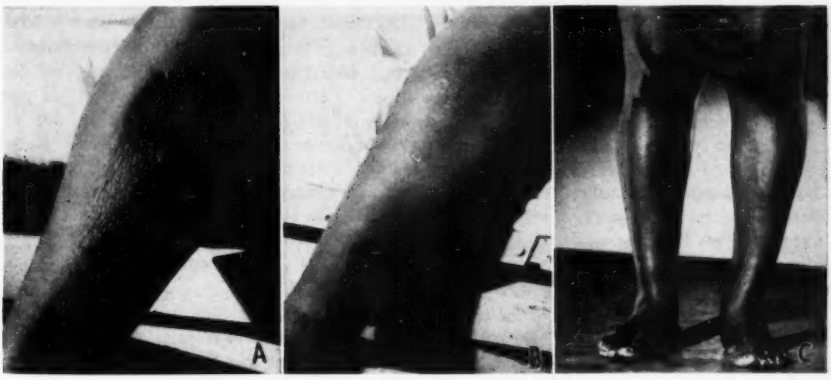

Fig. 1.—*A*, acute thrombophlebitis of anterior vein of leg in Negro woman. Superimposed second-degree burn by self-treatment. Redness and induration do not show. *B*, marked subsidence of all local findings with disappearance of pain and tenderness within 24 hours after intravenous infusion of trypsin. *C*, appearance one week after discharge from hospital. Only a small nontender firmness remains at the site (see text).

Case 1.—A Negro woman aged 30 was admitted with acute thrombophlebitis of the anterior vein of the left leg, of less than 24 hours' duration. An extreme degree of subjective pain prevented ambulation. Cellulitis and edema of the area surrounding the vein were augmented by a second-degree burn, the result of self-treatment at home. The rectal temperature was 101 F. Treatment consisted of bed rest, protection of the leg from bed sheets by means of bed span, and administration of 250,000 units of trypsin intravenously in 250 cc. of saline, 1 drop every two seconds. The same dose was repeated the next day. Forty-eight hours after admission there was complete subsidence of symptoms and local induration (Fig. 1). The temperature was 99 F. rectally. After one week the only residual was a nontender firmness at the site of the original lesion. After two weeks there remained only a slight residual edema below the lesion.

Case 4.—A white man, aged 62, underwent right lumbar sympathectomy for peripheral arterial occlusive disease. On the second postoperative day an acute thrombophlebitis of the left antecubital vein developed, with redness and cord-like hardening of the vein. This was apparently the result of an infusion of fluid during surgery. The temperature was 99.6 F. rectally. The following day the patient was given 250,000 units of trypsin intravenously in 250 cc. of saline, 1 drop every two seconds in the opposite antecubital vein. Eight hours after infusion the original

3. Innerfeld, I.: Personal communication to the authors. Fischer, M. M.: Personal communication to the authors.

tenderness had completely subsided and the vein was softer to palpation. However, a severer thrombophlebitis developed in the vein receiving the infusion than was originally present on the first side. The new thrombophlebitis was treated by warm packs and elevation and had almost completely subsided in 24 hours.

CASE 6.—A white man, aged 56, had known varicosities for 15 years. Pain, redness, and tenderness developed in a firm area of veins in the left posterior calf 24 hours before admission. The temperature was 98.8 F. rectally. Treatment consisted of bed rest, elevation of the legs and 250,000 units of trypsin in 250 cc. of isotonic sodium chloride solution given intravenously at the rate of 1 drop every two seconds. This dose was repeated daily for three days. After 48 hours, all induration, pain, and redness had disappeared, and the mass felt softer. After two more days of observation the mass of veins appeared to diminish in size. A bilateral vein ligation and stripping was done, and the involved segment was excised. Grossly it appeared no different from an organized type of thrombophlebitis.

CASE 11.—A white man, aged 65, had the chronic phlebitic syndrome for 15 years, complicated by parchment discoloration about the left lower leg. Redness, pain, and swelling had been present for 24 hours, with the development of a painful ulceration on the dorsum of the foot at the base of the second toe. On admission the temperature was 100.8 F. rectally. Upon examination this area and the second toe were rather cyanotic. There was an obvious acute thrombophlebitis and cellulitis related to the saphenous vein underlying the parchment area. One day of bed rest resulted in some diminution of the edema. Further treatment consisted of bed rest with bathroom privileges, and the administration of 250,000 units of trypsin in 200 cc. of water intravenously at the rate of 1 drop every two seconds. The same dose was repeated each day for four days. There appeared to be marked improvement over this period, consisting of disappearance of all pain after 48 hours and rapidly occurring changes of demarcation and cleansing of the ulcer base. A vein stripping was done the sixth day after admission. Within five more days the ulcer was healed, and the general color of the limb had improved.

CASE 5 (Courtesy of Dr. E. M. Marcus).—A 42-year-old white man had known varicosities for 10 years. Seven weeks prior to admission, heat, redness, and swelling developed in a mass of varices on the medial aspect of the left leg below the knee. This condition was treated with penicillin and bed rest, with subsidence within four days. Three days prior to admission the patient suffered a recurrence in the same area, which was severer than previously. The temperature on admission was 100.6 F. orally. Trypsin, 250,000 units, in 250 cc. of saline, 1 drop every two seconds, was given intravenously for four days. On the third day the greater saphenous vein on the affected leg became tenderer, palpable, and red up to the midthigh, indicating the extension of the thrombotic process proximally. After four days of trypsin therapy, a two-day period without treatment was allowed for the protein levels to readjust to normal. Another series of intravenous trypsin infusions was begun and continued for four additional days. During the interim period the thrombophlebitic process had extended to the fossa ovalis as a red tender cord, while the mass below the knee had cooled off and diminished in size. After the second course of four days of treatment, the redness and tenderness along the saphenous vein had subsided considerably, but the entire vein was palpable as a hard cord to the groin. The temperature had varied from 98.2 to 100 F. orally during the 10 day period. Ten additional days of observation were allowed, at which time it was decided that a saphenous vein ligation and excision be performed, since the thrombosis was still present. At surgery the thrombus was seen to stop 1 cm. from the saphenofemoral junction. Examination of the removed specimen revealed that the thrombus was the typical adherent inflammatory type, with no evidence of alteration by treatment.

CASE 8.—A 19-year-old Negro woman gave birth to a normal baby three weeks prior to the present admission. She had considerable postpartum bleeding which had not completely subsided at the time of present admission. There was a four-day history of severe pain of the entire left leg and thigh, especially anteromedially, extending to the left lower portion of the abdomen. The patient was admitted with a temperature of 104.6 F. rectally. On examination the entire left leg and the left lower abdominal quadrant were so tender that the lightest palpation could not be tolerated. The leg was mildly edematous. Previous treatment had consisted of administration of sulfisoxazole (Gantrisin) and penicillin for four days prior to admission. The diagnosis

was acute thrombophlebitis of the left femoral vein, probably extending into the left common iliac vein perhaps originating from the left adnexal veins. Treatment on admission consisted of giving 300,000 units of penicillin followed in four hours by injection of 250,000 units of trypsin intravenously in 250 cc. of saline, 1 drop every two seconds, and this same dose was repeated seven hours later. A single infusion was given each day for three subsequent days. The patient suffered intense pain for 48 hours after admission at which time the pain began to subside, but mild tenderness was still present. After four days all tenderness to deep palpation in the leg and abdomen had disappeared, and the temperature returned to normal. However, an extremely severe acute thrombophlebitis developed at the site of the infusion in the arm, and the temperature again rose to 101.6 F rectally. The arm was treated with warm compresses, elevation, and elastic support. Aureomycin was ordered by the resident. On the fifth day the patient was given a 500 cc. blood transfusion to correct her anemic state. The involved leg remained warmer than the normal leg and did not lose all of its edema despite the absence of pain. However, the leg did feel considerably softer than previously. The thrombophlebitis of the arm subsided in 48 hours. An elastic bandage was applied to the leg on the sixth day, and ambulation was begun. The patient was discharged on the 10th day, at which time there was a moderate degree of residual edema in the left leg and thigh. The patient was seen two weeks later as an outpatient, at which time the involved leg was still edematous but symptomless. Six weeks later it had the typical appearance of milk leg, although it was still slightly warmer than the normal leg.

Comment on Cases of Acute Thrombophlebitis.—It can be seen that the evidence of therapeutic efficacy of intravenous trypsin therapy in the cases presented is, of necessity, equivocal. Therefore the clinical course of these 10 patients was compared with that of a previous group of 10 comparable patients treated with conventional means, such as bed rest, warm packs, penicillin, and/or anticoagulant therapy. The only difference between these two groups of patients was the fact that in the patients treated with intravenous injections of trypsin, local pain, tenderness, and erythema disappeared within 48 to 72 hours in every case, while in the conventionally treated patients with acute thrombophlebitis, these symptoms took from 48 hours to 10 days to recede, with an average of 5 days. The significance of this difference obviously cannot be evaluated in such small samples.

The apparent anti-inflammatory effect of trypsin therapy seemed to be quite independent of the presence of the thrombus. In the cases in which superficial veins were palpable, the thrombus did not disappear with the disappearance of the inflammatory reaction. In the cases in which deep veins were involved the residual edema after subsidence of pain was taken as evidence that the thrombosis was still present.

The eventual disappearance of palpable thrombi in superficial vessels occurred after several weeks, and this time interval appeared not to differ appreciably from that in cases in which conventional treatment was given.

Chronic Thrombophlebitis.—Trypsin was administered intravenously to 20 adult patients with chronic thrombophlebitis ranging in duration from 10 weeks to 22 years. The ages of the patients ranged from 15 to 68 years. All cases were instances of lower extremity involvement. The duration of treatment with intravenous enzyme infusions ranged from one to eight days, although not more than four continuous days of treatment were permitted.

Our practice was to remove all previously worn elastic support and to allow the patient to be ambulatory, except for the several hours each day during which the infusion was being given. We noted that in practically every case of the eight patients so treated, a palpable softening of the edema resulted. The thigh circumferences diminished in every case, while the calf and ankle circumferences increased

in five cases and decreased in three. It usually took 48 to 72 hours for the tissues to soften, after which time we applied an elastic bandage. In the days following the application of the bandage, daily measurements were remarkably diminished as compared with previous measurements (Fig. 2).

We recognize that this regimen permitted more bed rest than each patient had been accustomed to prior to admission. Most of these patients had been actively employed or doing ambulatory housework. Consequently, another group of six patients with chronic thrombophlebitis was permitted a control period of three days consisting of three hours of compulsory rest in bed each afternoon. Measurements and degrees of softening of tissues were noted. The patients were then given intra-

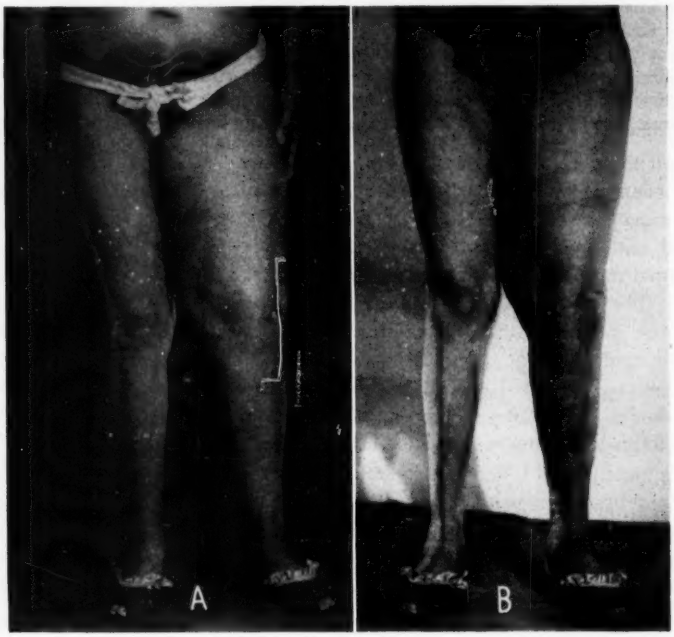

Fig. 2.—*A*, chronic thrombophlebitis following radiation therapy for inoperable carcinoma. *B*, after four days of intravenous trypsin therapy marked softening of the edema occurred. At this time an elastic bandage was applied. Illustration shows appearance of limb after two days of elastic compression (see text).

venous trypsin therapy to compare the results after three days of control observation with those at the termination of two to four days of treatment. Measurements were always made at marked levels on the thigh, calf, and ankle at approximately the same time of day.

The results of this program were interesting in that there was some softening and diminution in circumferential measurements in the involved extremities of all six patients following the three-day control period. These changes continued during the following two to four days of intravenous trypsin therapy, but we had the impression that there was not a sufficient difference between the results of each period of observation to establish a cause and effect relationship between the degree

of improvement and the trypsin therapy. In each instance elastic bandages were applied after completion of therapy and resulted in marked reduction in swelling.

We again noted, as in the acute cases, that those patients with chronic thrombophlebitis who had tenderness or pain along the course of the femoral vein experienced complete relief in 48 hours. The pain and tenderness did not return in any case during the outpatient follow-up period of up to six months, although swelling did recur.

Side-Effects.—In six instances (14.6%) the patient experienced a chill during or slightly after the infusion. In most cases the infusion was stopped when the chill occurred. However, in two cases the infusion was allowed to continue, with no apparent ill effects. The chill subsided within 15 minutes, similar to cases in which the infusion was stopped. This chill probably represents effects of the circulation of the products of proteolysis. In two instances severe abdominal cramps occurred toward the end of the infusion. It has been suggested that both the chills and the abdominal spasms may be the result of histamine reaction. Therefore in our last six cases we have added 50 mg. of diphenylhydramine (Benadryl) hydrochloride to the infusion mixture. None of these patients experienced either chills or cramps. Local symptoms at the site of infusion have already been mentioned. There were four instances in which treatment was discontinued after one or two days because the patient refused further therapy. Three patients refused further therapy after one day because of severe pain at the site of injection. The fourth patient refused infusions after the second day because of intense pain and burning in chronic leg ulcers, which pain he attributed to the infusion.

Contraindications.—Three contraindications were suggested by Innerfield's group. These were bleeding tendency, congestive heart failure, and liver failure. In congestive heart failure, cyanosis and methemoglobinemia have been noted to develop. This is probably based upon the fact that trypsinized red cells undergo a change in their oxygen-carrying capacity. It has been suggested that patients with poor liver function do not produce sufficient trypsin inhibitor to protect viable cells. It is conceivable that injured liver cells cannot regenerate intravascular proteins which may be hydrolyzed by trypsin. In addition to these contraindications we have felt that an open intestinal lesion, such as peptic ulcer or ulcerative colitis, as well as open pulmonary lesions, should logically be considered as contraindications because of the possibility of bleeding.

LABORATORY DATA

The blood of all patients who received intravenous injections of trypsin was tested before and after infusion. Among the tests run were erythrocyte count, leucocyte count, differential count, hemoglobin, erythrocyte sedimentation rate, coagulation time, prothrombin time, serum total protein, serum albumin, serum globulin, hematocrit, blood urea nitrogen and serum glucose. In isolated instances fibrinogen levels were followed. Routine urinalyses, including microscopic examinations, were done for all patients.

When the standard infusion of 250,000 units of trypsin in 250 cc. of isotonic sodium chloride solution was given at the rate of 1 drop every two seconds, no change in the above determinations occurred until the third or fourth day of continuous therapy. After four days the serum total protein dropped an average of 1.6 gm. per 100 cc. Most of this diminution represented a drop in serum globulin, although in an occasional instance there was a very small drop in serum albumin levels. No significant changes in any of the other determinations were noted in our patients. In our work with animals we noted that doses proportionally much larger than those used in human patients were necessary before changes in the blood coagulation mechanism occurred.

LABORATORY EXPERIMENTATION

Thrombi were produced in dogs by injecting 0.05 cc. (1 cc. equal to 1,000 units) of thrombin, U.S.P. (Thrombin Topical, Bovine Origin) into a 2 in. (5 cm.) segment of the femoral vein, or jugular vein, or external maxillary vein, between rubber-tipped bulldog clamps. A partially occluding cotton tie was placed on the central end of the segment to be clotted. This tie was made to occlude the vessel only partially, since we wished to allow maximal attack on the thrombus by the trypsin to be used. In all dogs subjected to this procedure, thrombi developed within a few minutes, and the clot remained in place in 9 of the 10 control animals after the clamps were removed. In the 10th animal we assumed that the clot had slipped through the noose.

Animals weighing from 10 to 15 kg. in which thrombi were produced in this manner were treated with intravenous infusions of trypsin using solutions ranging from 100,000 to 1,500,000 units. The rate of infusion varied from one drop every two seconds to two drops per second. Dilutions ranged from 1 : 1,000 to 1 : 100 in isotonic sodium chloride solution. Treatment was begun from 1 hour to 24 hours after formation of the clot, with a period of observation up to 72 hours after infusion.

In the first six dogs with thrombosed vessels treated with intravenous trypsin no clot was found in the involved area the next day. This finding duplicated that of Innerfield. However, in the next 10 animals we altered our procedure, inasmuch as we were concerned that the clot, being a rather loose structure, might have retracted and slipped through the noose. In this group of 10 animals, therefore, we placed the tie tightly. In none of these animals with the dosage range and mode of administration described above was there any gross effect upon the thrombus.

Four additional dogs were subjected to thrombus formation in a similar manner except that the noose was again placed loosely. Forty-eight hours after treatment these dogs were killed, and the branches of the pulmonary artery were carefully dissected. In each animal we found small thrombi in peripheral pulmonary artery branches.

Thus, our conclusion was that in the earlier experiments the intravenous infusion of trypsin, even in tremendous doses, had not actually dissolved the thrombus, but that the thrombus had passed onward without causing deleterious effects upon the animals.

In order to determine whether placing a tie tightly was an unfair test, since it may have deprived the thrombus of some surface action of trypsin, we performed the following experiment. In four dogs intravenous infusion of 500,000 units of trypsin in 200 cc. of isotonic sodium chloride solution was begun at the rate of 1 drop per second in a peripheral vein. Clots in the jugular vein were produced in the usual manner, and the tie was placed tightly on the central end. Forty-eight hours later the area was explored. In each instance there was extensive ecchymosis about the operative wounds as well as in other areas. The subcutaneous tissues about the vein in which the thrombus had been made were bloodshot, and free liquid blood was found between the tissue layers. The involved segment of vein was removed and was found to contain no clot. Pretreatment with smaller doses is presently under investigation.

We concluded from this experiment that the tie on the vein could be tight without deterring the action of trypsin. Furthermore, this experiment indicated that

blood pretreated with trypsin will form a clot, provided there is some clottable fibrinogen available at the time, but that such a clot will shed its cells and dissolve. When, however, a clot is formed prior to trypsin treatment the clot will not dissolve even if a state of complete afibrinogenemia supervenes. Thus, it would appear that in order for trypsin to dissolve a clot it must be incorporated within the clot by virtue of having been in the circulating blood at the time the clot was formed.

Further evidence to substantiate this point can be seen in Figure 3. The four test tubes represent blood drawn from a dog before, during, and after administration of 250,000 units of trypsin. Each tube of blood was placed in a water bath at 37.5 C. immediately after drawing. A clot formed in each test tube. However, the clot after infusion has shed its cells to become an unclottable sediment. Partial shedding of the blood during infusion occurs in proportion to the dose administered.

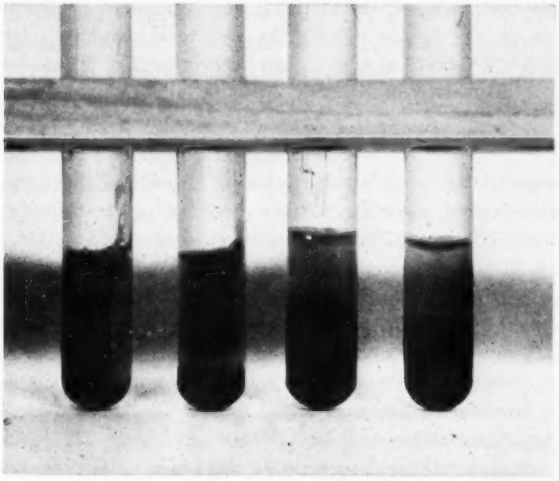

Fig. 3.—First test tube (left to right) represents normal clot retraction in blood of dog after 24 hours in water bath at 37.5 C. before trypsin therapy. The second tube represents partial dissolution of clot of blood drawn after infusion of 100,000 units of trypsin intravenously. This degree of shedding of cells from clot occurred within four hours after placement in water bath. The third tube represents further shedding of clot (clot has actually dropped into sediment of cells) after infusion of 200,000 units of trypsin intravenously. This tube has been in water bath for one hour. The fourth tube represents the complete dissolution of a clot in blood drawn after 250,000 units of trypsin was infused intravenously. The unclottable sediment of cells represents the appearance after 15 minutes in the water bath (see text).

When, however, the dose is insufficient, the clot will not completely disintegrate. Blood drawn from patients after receiving 250,000 units of trypsin intravenously does not exhibit this shedding phenomenon. This implies that 250,000 units in man is insufficient to cause a great enough drop in fibrogen level to alter the clottability of the blood.

Another experiment consisted of placing 1 cc. of canine or human blood in a test tube and allowing it to clot. Trypsin, 250,000 units, was dissolved in 3 cc. of isotonic sodium chloride. Thus, 1 cc. of this solution represented 83,300 units of trypsin. When 0.025 cc. (2,000 units) of this trypsin solution was added to 1 cc. of clotted blood we found that the clot was one-half digested in five hours, five-

sixths digested in 17 hours, and seven-eighths digested in 24 hours. Complete digestion of such a clot was obtained in 17 hours when 0.05 cc. of the concentrated trypsin solution was added to 1 cc. of clotted blood. Complete digestion was obtained in five hours when 0.1 cc. was added, and complete digestion was obtained in three and one-half hours when 0.3 cc. (25,000 units) of concentrated trypsin solution was added. This experiment is comparable to the well-known fact that trypsin solutions of high enough concentration will dissolve clots by direct contact. This principle has been amply demonstrated clinically by intrathoracic injections, etc.

Infusion of large doses of trypsin slowly administered to animals produced marked changes in the circulating blood, particularly in fibrinogen levels. The rate of hydrolysis of circulating clottable fibrinogen depends upon the rate of infusion. Using solutions of 200,000 units in 100 cc. isotonic sodium chloride, with an infusion rate of 2 drops every second, the clottable fibrinogen levels were reduced from a control average of 560 mg. to 340 mg. in 30 minutes and to a state of afibrinogenemia when 400,000 units of trypsin had been infused in 50 minutes. Restitution to preinfusion levels usually occurred in 24 to 48 hours.

COMMENT

We are aware of the many vagaries of a purely clinical therapeutic experiment, particularly with regard to such a variable entity as acute thrombophlebitis. The anti-inflammatory effect was the only apparently observed result of intravenous trypsin therapy with the doses employed.

The mechanism responsible for the anti-inflammatory effect is not known. It could conceivably be one or more of the following factors: (1) a purely fortuitous occurrence; (2) increased lymphatic drainage in the inflammatory area due to the mobilization of coagulated lymph; (3) increased capillary blood flow due to the mobilization of coagulated clumps of blood cells; (4) increased local phagocytosis, or (5) the activation of other enzyme systems.

We were reluctant to use larger doses, since our animal work indicated that one cannot expect to dissolve a preformed thrombus with intravenous trypsin administration, almost regardless of dose. Even in animals in which an afibrinogenemia was induced by giving trypsin intravenously, a preformed thrombus could not be dissolved in the 72 hours of observation. Our interpretation of this finding is based upon the supposition that the circulating substrates (clottable fibrinogen, antitrypsin, and other protein moieties) are hydrolyzed by the circulating infused trypsin, leaving only a small amount of active trypsin available for action upon a thrombus. This is rather dissimilar from the direct attack of high concentrations of trypsin upon a clot, for example, in the thorax. When, however, a certain amount of trypsin is incorporated within a clot, the addition of more trypsin intravenously will readily dissolve such a trypsinized clot.

This finding could theoretically serve as a basis for prophylaxis against postoperative thromboembolism. If dosages and time relationships can be established, it may be possible to infuse patients preoperatively with trypsin and to infuse more trypsin postoperatively. Thus, any clots formed in the veins of the lower extremities during or shortly after surgery would be formed with trypsinized blood. Such clots might then be dissolved by the postoperative infusions. Whether such a study

would be feasible would depend upon whether considerable bleeding at the operative site would occur, and whether wound healing would be affected. We are studying this phase of the problem at present.

Eagle and Harris showed, in 1937,[4] that small amounts of trypsin in vitro convert prothrombin to thrombin and thus produce a clot in oxalated blood in the absence of calcium, tissue extract, or platelet extract.

This could explain the local clotting during some infusions. Allen [5] has recently been able to produce temporary afibrinogenemia in the dog by injecting small amounts of thrombin over a period of time, rendering the blood incoagulable much the way trypsin does. Whether this mechanism comes into play in the action of trypsin on circulating blood is an interesting speculation.

SUMMARY

Solutions of crystalline trypsin were administered intravenously under certain conditions of dosage and rate of infusion to 10 patients with acute thrombophlebitis and to 20 patients with various sequelae to chronic thrombophlebitis. In addition, 11 patients with various unrelated conditions were given infusions with trypsin but were not included in this report. Up to the time of this report we have given 146 infusions of trypsin to patients.

Generalized side-effects were minimal, consisting of a transient chill in six cases and abdominal cramps in two cases. Local side-effects consisted mainly of a local irritation and thrombophlebitis at the site of infusion. These reactions have been minimized by certain measures taken in the more recently treated patients.

The main effect which we observed in treated patients appeared to be an anti-inflammatory one, resulting in the alleviation of pain, erythema, and tenderness. We were not able to produce actual lysis of existing thrombi. Intravenous administration of trypsin to patients for four days resulted in a drop in plasma total protein levels, mostly the result of decreased plasma globulin levels.

Experimental work in animals has demonstrated that much larger doses can be tolerated by dogs than were given to human beings. Effects upon the circulating blood of dogs were profound after infusion of large amounts of trypsin. The main effect was the diminution in circulating clottable fibrinogen. However, lysis of thrombi in animals could not be achieved unless some trypsin was infused prior to the formation of the thrombus and more trypsin was given afterward.

4. Eagle, H., and Harris, T. N.: Studies in Blood Coagulation: Coagulation of Blood by Proteolytic Enzymes (Trypsin, Papain), J. Gen. Physiol. **20**:543, 1937.

5. Allen, J. G.: Personal communication to the authors.

EXPERIMENTALLY PRODUCED ALTERATIONS OF HEPATIC BLOOD FLOW

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THE AMOUNT of blood flowing through the liver may be estimated using the principle of Fick. If sulfobromophthalein is infused at a constant rate in such amount as to keep the blood level constant, the rate of removal of this dye by the liver is assumed to be equal to the infusion rate. The concentration of sulfobromophthalein in the peripheral blood less the concentration in hepatic venous blood simultaneously withdrawn represents the amount of the dye withdrawn by the liver from each unit volume of the blood. The total amount of blood passing through the liver is calculated as the volume necessary for the removal of the amount of sulfobromophthalein being continuously injected. Bradley and his associates [1] have used this method for the study of hepatic blood flow in man. In their studies the samples of hepatic blood were removed through a catheter guided from a vein of the arm into the inferior vena cava and thence into one of the hepatic veins deep in the liver.

We have used this method for the study of hepatic blood flow in dogs under different experimental conditions affecting the liver. The results of these studies add further proof of the validity of the method and give quantitation to the changes in hepatic blood flow after (1) ligation of the hepatic artery, (2) occlusion of the portal vein, (3) occlusion of the abdominal inferior vena cava, (4) occlusion of both the portal vein and the inferior vena cava, and (5) production of experimental cirrhosis.

METHODS

Selected for this study were dogs which, after a few days of training in the laboratory, would not become restless or excited but would lie quietly on a table for two or three hours. The permanent cannula was placed in a hepatic vein (usually the vein from the large left lateral

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From the Section in Biochemistry (Dr. Bollman) and the Section of Surgical Research (Dr. Grindlay); Fellow in Experimental Medicine (Dr. Khattab), and Fellow in Surgery (Dr. Thors), Mayo Foundation, and Mayo Clinic.

1. (*a*) Bradley, S. E.: Conference on Liver Injury, Transactions of the 5th Meeting, September 26 and 27, 1946, New York, Josiah Macy, Jr., Foundation, 1947, p. 38. (*b*) Bradley, S. E.; Ingelfinger, F. J.; Bradley, G. P., and Curry, J. J.: Estimation of Hepatic Blood Flow in Man, J. Clin. Invest. **24**:890, 1945. (*c*) Bradley, S. E.; Ingelfinger, F. J.; Groff, A. E., and Bradley, G. P.: Estimated Hepatic Blood Flow and Hepatic Venous Oxygen Content in Cirrhosis of the Liver, Proc. Soc. Exper. Biol. & Med. **67**:206, 1948.

lobe of the liver) in the following manner. With the dog under ether insufflation anesthesia the right side of the thorax is opened along the 10th intercostal space. An incision in the diaphragm exposes the liver and the subdiaphragmatic portion of the abdominal inferior vena cava. A semirigid brass probe on which is threaded a polyvinyl tube (No. 20 transflex [2]) is introduced through a small incision in the vena cava. The probe is passed into the hepatic vein and pushed through the substance of the liver. It is then withdrawn until the distal end of the tube lies in the hepatic vein 3 or 4 cm. beyond the vena cava. The tube emerging from the liver is securely anchored to the surface of the liver over a small pledget of polyvinyl sponge,[3] and the end of the tube is passed through the abdominal wall. After surgical repair the animals remain in good condition, and the tube from the hepatic vein is available for withdrawal of blood and daily flushing of the tube with dilute solution of heparin.

Determinations of hepatic blood flow were made three or more days after operation, with the dog resting quietly on his back. A small polyethylene tube was passed through a needle in the ulnar vein. In normal dogs a priming injection of sulfobromophthalein (2 mg. per kilogram of body weight) was given through the tube, and this was followed by the continuous administration, from a mechanically driven syringe set to inject 40 ml. each hour, of a saline solution that contained 90 mg. of the dye for normal dogs weighing approximately 15 kg. In this way 1.5 mg. of sulfobromophthalein was injected each minute. At intervals of approximately 15 minutes, pairs of blood specimens were simultaneously withdrawn from the cannula in the hepatic vein and from the femoral artery by direct puncture or from a small catheter previously placed in the femoral artery. Five or six pairs of specimens were usually taken for each study. Dry heparin was used as an anticoagulant, and the sulfobromophthalein of the plasma was determined photometrically after the addition of sodium hydroxide. The amount of sulfobromophthalein given each minute divided by the difference, in milligrams per milliliter, between the sulfobromophthalein content of arterial plasma and that of the hepatic venous plasma indicated the volume of plasma passing through the liver each minute. The hematocrit value for hepatic venous blood was used for the calculation of the blood flow through the liver.

Ligation of the hepatic artery was accomplished in some dogs at the same time as cannulation of the hepatic vein. In others the hepatic artery was ligated several days to several months prior to cannulation of the hepatic vein, and in still others the hepatic vein was cannulated, and data were obtained on normal hepatic blood flow for 7 to 20 days prior to ligation of the hepatic artery, as well as for a period after ligation.

Three different types of ligation of the hepatic artery were performed: (1) ligation and section just proximal to its gastroduodenal branch, (2) ligation and section just distal to the gastroduodenal branch, and (3) complete ligation of all the hepatic branches of the hepatic artery. In the last-mentioned type, each branch of the hepatic artery is ligated at its entrance into each lobe of the liver, and all vessels in the gastrohepatic omentum except the portal vein and the common bile duct are ligated and divided. These dogs received penicillin daily for several days, and considerable necrosis of the liver occurred.

Occlusion of the portal vein and inferior vena cava was accomplished by application of partially constricting Cellophane bands about the veins two or more months prior to cannulation of the hepatic vein. The portal vein was constricted at its entrance into the liver, and the vena cava was constricted below the liver. In our experience the fibrous tissue band which develops under the Cellophane band constricts the portal vein and the vena cava to such degree that after two to three months the lumen does not exceed 3 mm. in diameter. Nevertheless, the vein was completely ligated at the time the hepatic vein was cannulated.

The cirrhotic dogs used in this study had been exposed to carbon tetrachloride vapor (20 mg. in each liter of air) for two hours three times each week for more than one year. The degree of cirrhosis was noted at operation and on microscopic examination of the biopsy specimens removed then and later when the experiment was terminated. Each of these animals had mild

2. Transflex tubing was furnished by Irvington Varnish and Insulation Company, Irvington, N. J.

3. Polyvinyl (Ivalon) sponge used in this study was furnished by the manufacturers, Ivano Inc., Chicago.

bilirubinemia, and there was considerable delay in the clearance of sulfobromophthalein. The degree of cirrhosis varied from that of a finely granular enlarged liver to that of a grossly nodular atrophic liver.

RESULTS

The calculations of hepatic blood flow seemed rather uniform if the injection rate was so regulated that it did not produce marked variations in the concentration of sulfobromophthalein in the peripheral blood. If the animals were quiet and resting, with no gross alterations of cardiac rate, the extraction ratio and the calculated blood flow were similar from day to day in the same animal. The variations in individual dogs observed at intervals over a six-week period were not more than 15%. The average determinations of blood flow are given in Table 1. The validity of the method was checked by the continuous injection into the portal vein of 1.5 mg. of sulfobromophthalein per minute after a priming dose and by the determination of blood flow at intervals beginning 20 minutes later. No appreciable arteriovenous differences were obtained between systemic blood and hepatic venous blood. This finding indicates that the liver removes sulfobromophthalein from the portal circulation and that there is no appreciable extrahepatic removal. If extrahepatic removal

TABLE 1.—*Average Values for Hepatic Blood Flow*

Condition	No. of Determinations	Ml./Kg./Min.
Normal	35	42.5 ± 0.9
Ligation of hepatic artery	17	40.0 ± 1.8
Cirrhosis (carbon tetrachloride)	7	37.0 ± 3.4
Occlusion of portal vein	2	19.3
Occlusion of inferior vena cava	2	45.5
Occlusion of inferior vena cava and portal vein	2	29.4

of the dye did occur, one would expect a greater concentration of it in the hepatic venous blood than in the peripheral blood. If the liver did not remove sulfobromophthalein at the same rate at which it was being injected, one would also expect a greater concentration to be found in the hepatic venous blood, associated with a rising peripheral concentration. Figure 1 shows the arteriovenous difference in the concentration of sulfobromophthalein when this substance was injected into the portal vein (V_1,A_1) and when it was injected into a peripheral vein (A_2,V_2).

The actual amount of blood passing through the liver is probably proportional to the cardiac output. Figure 2 indicates the hepatic blood flow of the same animal at different times when the cardiac rate was altered by administration of atropine. Similar variations have been observed after excitement and restlessness in animals under observation. For these reasons we have included in this study only those values obtained on well-trained quiet animals after almost complete recovery from their surgical procedures.

Determinations of hepatic blood flow after ligation of the hepatic artery tended to be slightly, but not significantly, lower than those obtained in normal dogs. The average of two or three sets of determinations made 3 to 10 days prior to ligation of the hepatic artery and the average of two or more sets of determinations made two or more days after ligation also indicate no appreciable change due to ligation (Table 2). Dogs 3 and 5 were studied over an interval of six weeks following liga-

tion of the hepatic artery. Variations of as much as 20% from the high to the low were obtained in the calculated hepatic blood flow in these animals, but the variations were sporadic and did not show any trend in relation to the time after opera-

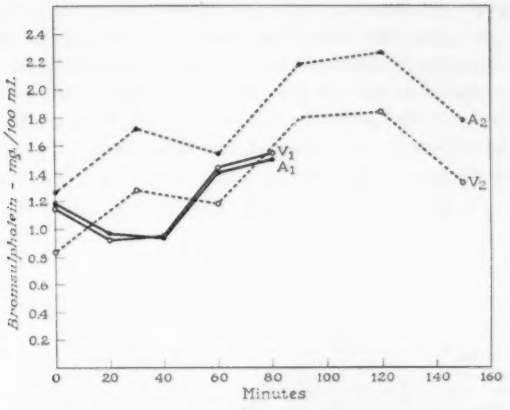

Fig. 1.—Concentration of sulfobromophthalein in arterial and hepatic venous blood at intervals beginning 20 minutes after a priming dose of 2 mg. per kilogram of body weight and the continuous injection of 1.5 mg. of the dye each minute. Curves A_1 and V_1 were obtained when the dye was injected into the portal vein, and curves A_2 and V_2 were obtained when it was injected into a peripheral vein.

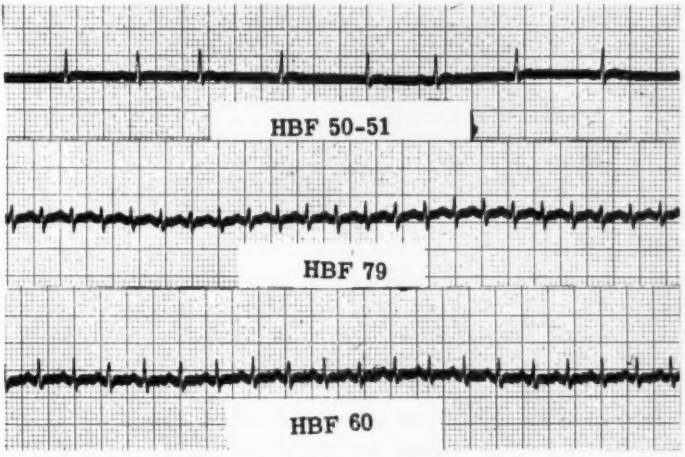

Fig. 2.—Electrocardiographic tracings from the same dog before and after receiving atropine. The indicated hepatic blood flow (*HBF*), in milliliters per kilogram of body weight per minute, was obtained during the same period as the electrocardiographic tracing.

tion. Other dogs in which the cannula was placed in the hepatic vein at the time of ligation of the hepatic artery are included in Table 1, as well as three dogs which were cannulated after recovery from complete ligation of the hepatic artery. One of these dogs, cannulated 200 days after ligation of the hepatic artery, showed an

average hepatic blood flow of 34 ml. per kilogram of body weight per minute. The left half of this animal's liver was markedly atrophic and the right half hypertrophic, so that the total weight was approximately normal. The dogs cannulated 42 and 55 days after complete ligation of the hepatic artery showed blood flows of 35.8 and 36.8 ml. per kilogram per minute. These livers were not grossly abnormal. At the termination of each experiment involving ligation of the hepatic artery, a barium gelatin mass was injected in the aorta post mortem. In every case, good and complete filling of the arterial vessels of the liver was obtained, and it was obvious that collateral circulation provided adequate channels for the filling of the hepatic artery.[4] The slight, but questionable, reduction of the blood flow of the liver which we observed following ligation of the hepatic artery should not be interpreted as indicating cessation of the arterial flow to the liver and an accompanying increase in the

TABLE 2.—*Hepatic Blood Flow Before and After Ligation of the Hepatic Artery*

Dog No.	Ligation	Ml./Kg./Min.	
		Before	After
1	Proximal	35.6	32.4
2	Proximal	39.6	34.4
3	Proximal (5 to 40 days)	43.2	46.0
4	Proximal	50.0	49.0
5	Proximal (5 to 45 days)	36.0	31.5
6	Distal	39.0	31.5

TABLE 3.—*Hepatic Blood Flow in Dogs with Cirrhosis of the Liver*

Dog No.	Cirrhosis	Ml./Kg./Min
1	Fine granular hypertrophic	48.3
2	Nodular atrophic	17.0
3	Nodular atrophic	30.0
	Hepatic artery ligated	27.6
4	Fine granular	39.8
	Hepatic artery ligated	34.4

rate of portal flow to the liver. We interpret these results as indicating no marked change in either the arterial or the portal blood flow to the liver.

In the cirrhotic dogs studied, the blood flow before the development of cirrhosis was not determined. The calculated blood flow after the development of cirrhosis in an average of seven dogs appeared to be only slightly less than that found in normal animals. However, the total blood flow through the liver appeared to correspond roughly with the size of the liver (Table 3). The blood flow was normal or slightly elevated in one animal with enlargement of the liver due to hypertrophic cirrhosis and was considerably reduced in animals with a small atrophic liver. Ligation of the hepatic artery was accomplished in two cirrhotic animals after preliminary determinations of hepatic blood flow had been made. Determinations made after ligation of the hepatic artery were not materially different from those made before ligation (Fig. 3).

4. Grindlay, J. H.; Mann, F. C., and Bollman, J. L.: Effect of Occlusion of the Arterial Blood Supply to the Normal Liver: An Experimental Study, A. M. A. Arch. Surg. **62**:806, 1951.

Calculated blood flow to the liver after complete occlusion of the portal vein appears to be definitely decreased, the average flow in one dog being 24.4 ml. per kilogram of body weight per minute and in the other, 14.3. Occlusion of the vena cava below the liver did not materially alter the rate of blood flow through the liver. In two dogs in which both the portal vein and the vena cava were occluded below the liver the rate of hepatic blood flow was lower than normal but definitely higher than in animals in which only the portal vein had been occluded. Additional studies of animals with occlusion of the portal vein and vena cava should be made before definite conclusions are reached.

COMMENT

The blood flow from the liver is the average of the flow from numerous sinusoids which vary considerably from time to time in their individual rates of blood flow. The flow of blood to the liver is dependent upon arterial pressure and flow, and on

Fig. 3.—Cirrhotic liver from a dog three weeks after intubation of the hepatic vein. The orifice of the plastic tube in the hepatic vein is 4 cm. from the vena cava.

the flow from the portal region. Both these sources of blood are relatively independent of the liver itself. The physiologic state of the animal must determine largely the amount of blood flowing to and from the liver.[5]

In some of their cases in which a catheter was used in the hepatic vein, Bradley and his co-workers [1b] noticed a vascular spasm which hampered the movement of the catheter in or out. The spasm of the vessel wall may influence the blood flow through the liver. Our use of indwelling tubes kept *in situ* for days or weeks minimizes the effect of immediate trauma. However, the constricting mechanism of the hepatic veins in dogs is very prominent and may come into play under a number of physiologic variations. We have usually intubated the large left lobe of the liver and

5. Grindlay, J. H.; Herrick, J. F., and Mann, F. C.: Measurement of the Blood Flow of the Liver, Am. J. Physiol. **132**:489, 1941.

considered the sample as representative of hepatic venous blood. Bradley and co-workers found that the uptake of sulfobromophthalein by the different lobes of the liver varies somewhat but that the variation does not exceed 20%.

A small amount of sulfobromophthalein is excreted in the bile and reabsorbed into the circulation,[6] but this amount is insignificant with the small doses used in the study of blood flow. Our studies of sulfobromophthalein excretion in dogs which had a biliary fistula and which received 2 mg. of the dye per minute indicated that about a sixth of the total amount given was excreted in the bile. In the actual determination of blood flow, however, reabsorbed sulfobromophthalein from the gastrointestinal tract did not enter into the calculations and did not affect the results of the determination. The amount of dye excreted in the urine of dogs receiving 1.5 mg. per minute does not exceed 0.5% of the amount injected over the course of an hour. Cohn and his associates [7] showed that in the absence of the liver, the gastrointestinal tract, and the kidneys, sulfobromophthalein was removed at constant rates from the blood stream. They calculated that the peripheral tissues of the dog were capable of removing the dye 25 to 30% as rapidly as were the tissues of animals possessing the liver and gastrointestinal tract. In a later paper, Cohn and co-workers [8] found that the removal of intravenously injected sulfobromophthalein was greater at high concentrations of the dye in the plasma than at low concentrations. Mason and co-workers [9] found that a large fraction of the initial priming dose of the dye was quickly removed from the vascular compartment, probably by saturation of the cells of the reticuloendothelial system. Subsequently no further uptake of the dye occurs by this means, or the rate of transfer of the dye from this system to the liver cells attains a constant rate. Bradley [10] reviewed the subject of extrahepatic removal of the dye and decided that it was insignificant when the concentration in the blood was kept below 2 mg. per 100 cc. He also carried out studies on eviscerated dogs and showed that the total removal of sulfobromophthalein, after the liver was removed, was less than 5% of the control values.

SUMMARY

The determination of hepatic removal of sulfobromophthalein from the blood of the hepatic vein and the peripheral circulation during a constant injection of this dye appears to be a satisfactory method of estimating hepatic blood flow in dogs. Two or more days after ligation of the hepatic artery the blood flow through the liver is not materially altered. In cirrhotic animals the rate of blood flow through the liver

6. Lorber, S. H., and Shay, H.: Entero-Hepatic Circulation of Bromsulphalein, J. Clin. Invest. **29**:831, 1950.

7. Cohn, C.; Levine, R., and Streicher, D.: The Rate of Removal of Intravenously Injected Bromsulphalein by the Liver and Extra Hepatic Tissues of the Dog, Am. J. Physiol. **150**:299, 1947.

8. Cohn, C.; Levine, R., and Kolinsky, M.: Hepatic and Peripheral Removal Rates, in the Dog, for Intravenously Injected Bromsulphalein, Am. J. Physiol. **155**:286, 1948.

9. Mason, M. F.; Hawley, G., and Smith, A.: Application of the Saturation Principle to the Estimation of Functional Hepatic Mass in Normal Dogs, Am. J. Physiol. **152**:42, 1948.

10. Bradley, S. E.: Clinical Aspects of Hepatic Vascular Physiology, in Liver Injury, Transactions of the 9th Conference, April 27 and 28, 1950, New York, Josiah Macy, Jr., Foundation, 1951, p. 71.

is roughly proportional to the size of the liver and is not materially altered by ligation of the hepatic artery. Complete occlusion of the portal vein reduces the flow of blood through the liver to about half the value found in the normal resting dog.

DISCUSSION

DR. JACOB K. BERMAN, Indianapolis: I congratulate Drs. Bollman and Grindlay on their excellent piece of work. It is indeed outstanding and will do much to clarify previous research on liver circulation. Burton-Opitz, in 1911, and MacLeod and Pearce, in 1914, tried to solve the moieties of hepatic blood flow and their variations. They concluded that about two-thirds of the blood comes from the portal vein and one-third from the hepatic artery. However, they did not cannulate the dogs, as did Drs. Bollman and Grindlay, and they did not have the long periods of observation after ligation of the hepatic artery.

I am sure that the clinical application of this basic research will have varied interpretations by members of this audience. However, to me this work implies that one may ligate the hepatic artery in the normal dog or in the experimentally produced cirrhotic dog without materially affecting the blood flow through that organ. But, I believe that in advanced portal cirrhosis in man with hepatic circulatory decompensation the problem is very different. Here we believe hepatic arterial pressure may seriously impede the onward flow of portal blood.

Our present concept is that in late or advanced atrophic cirrhosis with a hard shrunken liver, the entire splanchnic bed, including the abdominal wall, is converted into what might be termed a huge cavernous hemangioma. In order to substantiate this concept, I should like to show a few slides, and I shall have only time enough to comment on one part of their context. These graphs are composite figures based on our own findings and on those of many other investigators.

(Slide) This diagram demonstrates the pressure gradients in the venous system of the normal and the cirrhotic liver. I call your attention to one extremely important finding. The hydrostatic pressure in the normal mesenteric, portal, sinusoidal, and hepatic venous streams progressively decreases from about 26 to 1 mm. Hg. In early portal cirrhosis there is an abrupt fall in the pressure in the sinusoids and the hepatic veins despite the great increase in the mesenteric and portal venous pressure. However, in late atrophic cirrhosis, hepatic venous pressure is greatly augmented and is never below the highest normal portal pressure. This, we believe, to be due to the many collaterals which pour their contents into the hepatic veins.

(Slide) This is a diagram depicting the arteriovenous oxygen differences in the systemic and portal systems. Oxygen concentrations vary greatly in animals and in man from hour to hour. By recording the arteriovenous differences we have a more uniform and constant figure to study. The normal systemic arteriovenous difference varies between 4 and 7 vol. %. The arteriovenous difference of the portal system varies roughly inversely with the pressure. Thus the oxygen difference between the hepatic artery and the portal vein is about 3½ to 6 vol. %, whereas the oxygen difference between the hepatic artery and the hepatic veins is 2½ to 4½ vol. %. In late atrophic cirrhosis the hepatic arterial-portal venous difference is less, ranging between 3 to 5 vol. %, but the arterial hepatic venous difference is greater due, we believe, to three factors: (1) an increased oxygen uptake by the ischemic liver cells, (2) a sluggishness of flow in the splanchnic bed permitting more complete deoxygenation by the liver, spleen and gastrointestinal tract, and (3) a diversion of the oxygenated blood into the systemic circulation. All of this means that oxygenated blood seems to be getting into the portal system without traversing the capillary bed.

(Slide) This is exemplified further by a study of the arteriovenous difference in advanced portal cirrhosis between the femoral artery and the antecubital veins and the large collateral veins in the abdominal wall. The oxygen difference between the femoral artery and the antecubital vein in patients with portal cirrhosis is 4 to 7 vol. %; whereas it is only 0.9 to 1.8 vol. % between the femoral artery and the collateral venous channels in the abdominal wall.

How does the oxygen get to these collaterals? We believe that it must be through some shunt mechanism.

(Slide) This is a photograph of the abdominal wall of a 36-year-old man whose case I reported in the December 1952 issue of the *Wisconsin Medical Journal*. I believe this is the

first case of its kind to be recorded. He was injured in an explosion in March, 1951, by a large fragment of steel which struck him in the abdomen, producing a deep laceration in the right lobe of the liver. This was repaired, and the patient recovered without any apparent complication. Ten months later, that is, in January, 1952, he came to the Veterans Administration Hospital, Fort Benjamin Harrison, with ascites and bleeding varices, of which he ultimately died. We have postmortem slides of that liver.

(Slide) Abdominal exploration, which was done in February, 1952, showed bleeding varices, ascites, and a liver which was grossly normal except for a small scar in the right lobe. Biopsies taken at the time of exploration disclosed no pathological changes. At autopsy the entire liver was found to be normal, with the exception of a small guileless scar, deep in the right lobe close to the porta hepatis but not involving it.

(Slide) After it was examined, and the venous tree injected with iodopyracet (Diodrast) we found the following significant changes. When the opaque material was injected into the hepatic vein it communicated freely with the portal vein and the hepatic artery. In fact, a clamp was placed on the hepatic artery to prevent complete loss of the contrast material.

(Slide) When iodopyracet was injected into the portal vein we found this postmortem clot. The hepatic artery had to be clamped because when we injected the material into the portal vein it ran out through the hepatic artery. This had not been observed by us during our many perfusion experiments on cirrhotic livers. There was no obstruction anywhere in the portal or hepatic venous system to account for this man's symptoms. This, we believe, is a case of traumatic portal cirrhosis produced by an injury deep in the liver and probably, although we could not prove it by microscopic examination, caused by shunts between the hepatic artery and the hepatic veins increasing the pressure in the latter and producing the clinical picture of portal cirrhosis with ascites and bleeding varices. The hepatic arterial and portal venous communications completed the pathological shunts which are ordinarily encountered in late atrophic cirrhosis.

Dr. Dale Habegger and I are presently engaged in trying to reproduce this picture in animals by placing temporary clamps on the hepatic artery and portal vein, cutting deep in the liver, and making anastomoses between the hepatic arterial branches and hepatic veins. In this way we hope to be able to duplicate the pathological processes which cause vascular decompensation in the atrophic scarred Laennec-type cirrhosis.

News and Comment

ANNUAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

New York, June 1-5, 1953

The following portion of the program of the American Medical Association Scientific Session relating to surgery will be of interest to readers of this Journal.

GENERAL SCIENTIFIC MEETINGS

GRAND BALLROOM, COMMODORE HOTEL

Monday, June 1—9 a. m.

ALPHONSE MCMAHON, Member of Council on Scientific Assembly, Presiding

9:00 a. m. **Pregnancy, Lactation, Growth and Aging as Special Stress Factors on** Nutritional Processes

TOM D. SPIES, Scientific Director, Nutrition Clinic of Hillman Hospital, Birmingham, Ala.

9:45 a. m. **Treatment of Hodgkin's Disease and the Lymphosarcoma**

OVID O. MEYER, Professor of Medicine, University of Wisconsin, Madison, Wis.

10:30 a. m. **Tissue Culture in the Service of Clinical Medicine**

C. M. POMERAT, Professor of Cytology and Director of Tissue Culture Laboratory, University of Texas Medical Branch, Galveston, Texas

11:15 a. m. **Medical Management of Hypertension**

HENRY A. SCHROEDER, Associate Professor of Medicine, Washington University School of Medicine, St. Louis

Monday, June 1—2 p. m.

MICHAEL E. DEBAKEY, Member of Council on Scientific Assembly, Presiding

2:00 p. m. **Postoperative Adrenal Insufficiency in Patients Who Have Taken Cortisone Prior to Surgery**

F. RAYMOND KEATING JR., Associate Professor of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn., and

WARREN A. BENNETT, Assistant Professor of Pathology, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

2:45 p. m. **Today's Medicine in Underdeveloped Areas**

JOHN Z. BOWERS, Dean, College of Medicine, University of Utah, Salt Lake City, Utah

3:30 p. m. **Interdependence of the Medical Profession and the Pharmaceutical Manufacturers**

ELMER L. SEVRINGHAUS, Director of Clinical Research, Hoffmann-LaRoche, Inc., Nutley, N. J.

4:15 p.m. **Treatment of Advanced Mammary Cancer**

CHARLES B. HUGGINS, Director of the Ben May Laboratory for Cancer Research, University of Chicago, Chicago, and

THOMAS L-Y. DAO, Instructor in Surgery, University of Chicago, Chicago

Friday, June 5—9 a. m.

TODAY'S MEDICINE FOR TOMORROW'S PATIENT

CHARLES GORDON HEYD, Past President, American Medical Association, Moderator

9:00 a. m. **Atomic Medicine for Tomorrow's Patient**

JOHN Z. BOWERS, Dean, College of Medicine, University of Utah, Salt Lake City

How Can We Protect the Youth of Today Against the Heart Ills of Tomorrow?

PAUL D. WHITE, Past President, American Heart Association, Boston

Today's Chemicals for Tomorrow's Patient

ARTHUR P. RICHARDSON, Associate Dean, Emory University School of Medicine, Emory University, Ga.

Today's Treatment of the Premature Infant

WOODRUFF L. CRAWFORD, Assistant Clinical Professor of Pediatrics, University of Illinois College of Medicine, Rockford, Ill.

Today's Treatment for the Gastric and Duodenal Ulcer Patient

ARTHUR W. ALLEN, Past President, American Surgical Association, Boston

The Role of the Hospital in the Medical Care of Tomorrow's Patient

ALBERT W. SNOKE, Director, Grace-New Haven Community Hospital, New Haven, Conn.

10:15 a. m. **Discussion from the floor**

SECTION ON ANESTHESIOLOGY

JADE ROOM, WALDORF-ASTORIA HOTEL

Tuesday, June 2—9 a. m.

BUSINESS MEETING

REPORT OF DELEGATE

Endotracheal Anesthesia in Children for Tonsillectomy and Adenoidectomy and for Other Surgical Procedures of Longer Duration

JOHN W. PENDER, Rochester, Minn.

Discussion to be opened by SAMUEL L. LIEBERMAN, Buffalo; A. H. KORNBLAU, Jamaica, N. Y., and ROBERT M. SMITH, Boston

Renal Function During Anesthesia and Operation E. M. PAPPER, New York

Discussion to be opened by URBAN H. EVERSOLE, Boston, and CLARENCE L. P. HEBERT, Staten Island, N. Y.

Studies on Body Temperature in Anesthetized Man

ROBERT E. CLARK, LOUIS R. ORKIN, and E. A. ROVENSTINE, New York

Discussion to be opened by MEYER SAKLAD, Providence, R. I., and HENRY K. BEECHER, Boston

Histological Changes in Nerve and Soft Tissues After Injection of Various Local Anesthetic Substances

WALTER H. MANNHEIMER, JOHN ADRIANI, and PHILIP PIZZOLATO, New Orleans

Discussion to be opened by DANIEL C. MOORE, Seattle, and ALBERT M. BETCHER, New York

Cerebral Edema and Its Relationship to Barbituric Acid Poisoning

LLOYD H. MOUSEL, Seattle

Discussion to be opened by RAYMOND F. COURTIN, Worcester, Mass.; RICHARD H. BARRETT, Hanover, N. H., and DONALD E. HALE, Cleveland

Spinal Anesthesia Prolonged for Fourteen, Eleven, and Seven Days Respectively

F. PAUL ANSBRO, FRANCIS S. LATTERI, and ALBERT E. BLUNDELL, Brooklyn

Discussion to be opened by MAX S. SADOVE, Oak Park, Ill., and MORRIS J. NICHOLSON, Boston

Wednesday, June 3—9 a. m.

ELECTION OF OFFICERS

Clinical Evaluation of Dextran as a Plasma Volume Expander

HARRY W. BOWMAN, Bethlehem, Pa.

Discussion to be opened by I. S. RAVDIN, Philadelphia, and SAM F. SEELEY, Washington, D. C.

Postoperative Nausea and Vomiting

MARGARET A. CLARK, and CHARLES D. ANDERSON, Oakland, Calif.

Discussion to be opened by ROBERT L. PATTERSON, Pittsburgh, and B. B. SANKEY, Cleveland

Chairman's Address: The Anesthesiologist's Responsibility to the Patient

ROLLAND J. WHITACRE, Cleveland

The Pharmacologic Basis for the Rational Use of Thiopental in Clinical Anesthesia

JOHN J. BURNS, BERNARD B. BROADIE, and PHILIP A. LIEF, New York

Discussion to be opened by BENJAMIN E. ETSTEN, Boston, and JOHN W. UZMANN, Albuquerque, N. Mex.

Therapy of Narcotic Poisoning With and Without Analeptics

JAMES E. ECKENHOFF, Philadelphia, and WILLY H. DAM, Copenhagen, Denmark

Discussion to be opened by ROBERT W. LYKINS, Portsmouth, Va., and HOWARD M. AUSHERMAN, Chattanooga, Tenn.

Thursday, June 4—9 a. m.

Recent Advances in Obstetrical Analgesics

BERNARD E. CAPPE, Jamaica, N. Y., and IRVING M. PALLIN, Brooklyn

Discussion to be opened by ALLAN A. GENTLING, Fort Worth, Texas, and VIRGINIA APGAR, New York

Complications Associated with the Use of "Controlled Hypotension" in Anesthesia

L. JENNINGS HAMTON, New Haven, Conn., and DAVID M. LITTLE JR., Stamford, Conn.

Discussion to be opened by STEVENS J. MARTIN, Hartford, Conn., and SCOTT M. SMITH, Salt Lake City

Hexamethonium Salts as an Aid to the Orthopedic Surgeon

RANALD J. M. STEVEN, and RALPH M. TOVELL, Hartford, Conn.

Discussion to be opened by FRANCIS F. FOLDES, Pittsburgh, and ROGER W. RIDLEY, Rochester, Minn.

Placental Transmission of D-Tubocurarine Chloride from Mother to Fetus

CHARLES B. PITTINGER and LUCIEN E. MORRIS, Iowa City

Discussion to be opened by RALPH T. KNIGHT, Minneapolis, and LLOYD E. LARRICK, Cincinnati

The Advantages and Complications of Tracheotomy

HAMILTON S. DAVIS and HENRY E. KRETCHMER, Cleveland, and ROGER BRYCE-SMITH, Oxford, England

Discussion to be opened by J. EARL REMLINGER JR., Evanston, Ill., and DONALD L. BURDICK, New York

Tobacco Bronchitis: An Anesthesiologic Study BARNETT A. GREEN, Brooklyn

Discussion to be opened by ALVAN L. BARACH, New York, and HENRY S. RUTH, Philadelphia

SECTION ON SURGERY, GENERAL AND ABDOMINAL

TOWN HALL

Tuesday, June 2—2 p. m.

The Management of Remaining Common Duct Stones by Various Solvents and the Biliary Flush Regimen

R. Russell Best, John A. Rasmussen and Carlyle Wilson, Omaha

Discussion to be opened by Waltman Walters, Rochester, Minn., and Frank Glenn, New York

Chronic Pancreatitis and Associated Stenosis of the Common Bile Duct: Treatment by Roux Y Choledochojejunostomy Frank F. Allbritten Jr., Philadelphia

Discussion to be opened by John B. Mulholland, New York, and Jonathan E. Rhoads, Philadelphia

Bilateral Adrenalectomy for Severe Hypertension

Ralph F. Bowers, Memphis, Tenn.

Discussion to be opened by Harold Zintel and William A. Jeffers, Philadelphia

Surgery of the Elderly John D. Stewart, Buffalo

Discussion to be opened by Warren H. Cole, Chicago

Pancreatic Considerations in Gastric Surgery Kenneth W. Warren, Boston

Discussion to be opened by G. Gavin Miller, Montreal, Canada, and Robert Coffey, Washington, D. C.

The Surgical Management of Arteriosclerotic Abdominal Aortic Aneurysms

J. M. Waugh, J. H. Grindlay, J. W. Kirklin, and C. R. Openshaw, Rochester, Minn.

Discussion to be opened by Arthur H. Blakemore, New York, and Geza de Takats, Chicago

Wednesday, June 3—2 p. m.

ELECTION OF OFFICERS

Chairman's Address I. Ridgeway Trimble, Baltimore

The Treatment of Cardiac Arrest and Ventricular Fibrillation

Julian Johnson, Philadelphia

Discussion to be opened by Claude Beck, Cleveland, and E. M. Papper, New York

The Treatment of Interauricular Septal Defects Robert E. Gross, Boston

Some Experiences with the Mechanical Heart in Human Surgery

F. D. Dodrill, Detroit

The Rational Use of Antibiotic Therapy in the Control of Surgical Infections

Frank L. Meleney, New York

Discussion to be opened by William R. Sandusky, Charlottesville, Va.

Thursday, June 4—2 p. m.

The Modern Treatment of Hirschsprung's Disease Orvar Swenson, Boston

Discussion to be opened by C. Everett Koop, Philadelphia, and Robert B. Hiatt, New York

Hypotensive Anesthesia for Radical Pelvic and Abdominal Surgery

C. Paul Boyan, New York

Discussion to be opened by Alexander Brunschwig, New York

Nutrition Following Gastric Operations for Peptic Ulcer

Robert M. Zollinger and E. H. Ellison, Columbus, Ohio

The Low Sodium Syndrome in Surgical Patients: Deficiency, Maldistribution or Dilution? FRANCIS D. MOORE, Boston

Discussion to be opened by H. T. RANDALL, New York, and JAMES D. HARDY, Memphis, Tenn.

The Application of Intestinal Antisepsis in Surgery EDGAR J. POTH, Galveston, Texas

Discussion to be opened by WARFIELD M. FIROR, Baltimore, and ROBERT A. SCARBOROUGH, San Francisco

Current Procedure in the Management of Small Bowel Obstruction

CLARENCE DENNIS, New York

Discussion to be opened by LELAND S. MCKITTRICK, Boston, and JOHN R. PAINE, Buffalo

SECTION ON UROLOGY

NORTH BALLROOM, HOTEL ASTOR

Tuesday, June 2—9 a. m.

The Management of Kidney Injuries

HARRY M. SPENCE, SIDNEY S. BAIRD, and ELGIN W. WARE, Dallas, Texas

Injuries of the Ureter

HAMILTON W. MCKAY, H. HAYNES BAIRD, and HOMER R. JUSTIS, Charlotte, N. C.

Bladder Injuries: Diagnosis and Treatment GEORGE C. PRATHER, Brookline, Mass.

The Management of Urethral Injuries WILLIAM J. BAKER, Chicago

Discussion to be opened by MOSES SWICK, New York

The Male Factors in Infertility. JOHN MACLEOD, New York

Mechanical Aspects and Surgical Corrections of Male Sterility

VINCENT J. O'CONOR, Chicago

Endocrinological Aspects of Male Infertility PETER M. F. BISHOP, London, England

Discussion to be opened by ROBERT S. HOTCHKISS, New York, and NORRIS J. HECKEL, Chicago

Tuesday, June 2—2: 30 p. m.

Discussion of Section Exhibits in Booths in Scientific Exhibit at Grand Central Palace

Wednesday, June 3—9 a. m.

ELECTION OF OFFICERS

Chairman's Address: The Effect of Supervoltage Rotational X-Ray Therapy on Extensive Carcinoma of the Bladder EARL E. EWERT, Boston

The Clinical Significance of Hematuria CHARLES C. HIGGINS, Cleveland

Discussion to be opened by LAURENCE F. GREENE, Rochester, Minn.

Anatomy and Physiology of the Urinary Bladder

CHARLES N. DUNCAN and REX E. VAN DUZEN, Dallas, Texas

Cystometry, the Reflex Hammer of Bladder Activity

REED M. NESBIT and WILLIAM C. BAUM, Ann Arbor, Mich.

The Clinical Management of Urinary Retention in Children

TRACY O. POWELL and HAROLD N. EDELBROCK, Los Angeles

Vesical Neck Dysfunction Due to Long-Standing Cord Injury

GERSHOM J. THOMPSON, Rochester, Minn.

Wednesday, June 3—2: 30 p. m.

Discussion of Section Exhibits in Booths in Scientific Exhibit at Grand Central Palace

Thursday, June 4—9 a. m.

The Treatment of Urinary Tract Infections DEAN PARKER, Seattle

The Management of Vesicourethral Dysfunction in Women
RUSSELL CARSON, Fort Lauderdale, Fla.

The Management of Bladder Irritation in the Female
HAROLD A. O'BRIEN, Dallas, Texas

Discussion to be opened by ORMOND S. CULP, Rochester, Minn.

Radical Prostatectomy JOHN K. LATTIMER and ARCHIE L. DEAN, New York

Malignant Tumors of the Testis
J. C. KIMBROUGH and F. E. COOK, Washington, D. C.

Discussion to be opened by JOHN A. TAYLOR, New York

Treatment of Hypospadias FRED Z. HAVENS, Rochester, Minn.

Discussion to be opened by VICTOR MARSHALL, New York

Thursday, June 4—2: 30 p. m.

Discussion of Section Exhibits in Booths in Scientific Exhibit at Grand Central Palace

SECTION ON ORTHOPEDIC SURGERY

MODERNE ROOM, BELMONT PLAZA HOTEL

Tuesday, June 2—9 a. m.

The Early Roentgenographic Signs of Perthes' Disease TOM OUTLAND, Harrisburg, Pa.

Discussion to be opened by CHARLES W. GOFF, Hartford, Conn., and M. BECKETT HOWORTH, New York

Panastragalar Arthrodesis WALTER S. HUNT JR. and HUGH A. THOMPSON, Raleigh, N. C.

Discussion to be opened by ROBERT L. PATTERSON, New York, and ROBERT J. JOPLIN, Boston

The Treatment of Infection After Insertion of an Intra-Medullary Nail
J. ALBERT KEY, FRED C. REYNOLDS, and JAMES O. LOTTES, St. Louis

Discussion to be opened by DANA M. STREET and HUGH SMITH, Memphis, Tenn.

The Effects of Extensive Radiation on the Healing of Fresh Fractures
AUGUST W. SPITTLER, JOSEPH W. BATCH, and BEN A. RUTLEDGE, Washington, D. C.

Discussion to be opened by EDGAR M. BICK, New York, and A. R. SHANDS JR., Wilmington, Del.

The Triceps Surae Syndrome in Cerebral Palsy LENOX D. BAKER, Durham, N. C.

Discussion to be opened by CHARLES N. PEASE, Chicago, and FREDERICK L. LIEBOLT, New York

Du Puytren's Contracture of the Foot
HERBERT E. PEDERSEN and A. JACKSON DAY, Dearborn, Mich.

Discussion to be opened by LEE C. SCHLESINGER, New Orleans, and EMANUEL B. KAPLAN, New York

Wednesday, June 3—9 a. m.

ELECTION OF OFFICERS

Early Management of the Injured Hand
JOSEPH D. GODFREY and WILLIAM D. DUGAN, Buffalo

Discussion to be opened by J. WILLIAM LITTLER, New York, and GEORGE O. EATON, Baltimore

Spondylolisthesis PAUL C. COLONNA, Philadelphia

Discussion to be opened by FREDERIC C. BOST, San Francisco, and JOHN R. NORCROSS, Chicago

Chairman's Address: Has a Solution for the "Unsolved Fracture" Been Found?
H. RELTON MCCARROLL, St. Louis

Problems in Management of Fractures of the Shaft of the Tibia
MILTON S. THOMPSON, Fort Sam Houston, Texas

Discussion to be opened by JOHN S. THIEMEYER, Portsmouth, Va., and FRANK E. STINCHFIELD, New York

Flake Fracture of the Astragalus BRUCE J. BREWER, Milwaukee

Discussion to be opened by NICHOLAS J. GIANNESTRA, Cincinnati, and WALTER P. BLOUNT, Milwaukee

Thursday, June 4—9 a. m.

PANEL DISCUSSION: ARE BONE SARCOMAS CURABLE?
BRADLEY E. COLEY, New York, Moderator

Panel Members: C. HOWARD HATCHER, Chicago; MURRAY M. COPELAND, Washington, D. C.; LAUREN V. ACKERMAN, St. Louis; J. VERNON LUCK, Los Angeles; and NORMAN L. HIGINBOTHAM, New York

SECTION ON OBSTETRICS AND GYNECOLOGY

TOWN HALL

Tuesday, June 2—9 a. m.

Spinal Anesthesia in Caesarean Section: A Critical Analysis of Some 1,200 Cases with No Maternal Mortality DONALD W. DECARLE, San Francisco

Discussion to be opened by ROBERT A. COSGROVE, Jersey City, N. J., and EDWARD C. ALLEN, Boston

The Intrapartum Initiation of Lactation Control with a Single Dose of a Long-Acting Androgen (Testosterone Cyclopentylpropionate)

SAMUEL M. DODEK, JOSEPH M. FRIEDMAN, PETER A. SOYSTER, and HARVEY L. MARCELLUS, Washington, D. C.

Discussion to be opened by ROBERT B. GREENBLATT, Augusta, Ga.

An Experience of 27 Years in the Therapeutic Administration of Low Voltage X-Rays to the Pituitary and Ovaries in the Treatment of Female Sterility
IRA I. KAPLAN, New York

Discussion to be opened by LEON ISRAEL, Philadelphia

Periodic Examination of the Female Breasts and Pelvic Organs: Report of a 15 Year Research on the Control of Cancer

CATHARINE MACFARLANE, Philadelphia; MARGARET C. STURGIS, Wynnewood, Pa., and FAITH S. FETTERMAN, Philadelphia

Discussion to be opened by GRAY H. TWOMBLY, New York

Improved Fertility and Prevention of Abortion After a Liver-Hormonal Regimen
S. J. GLASS and M. L. LAZARUS, Beverly Hills, Calif.

Discussion to be opened by MORTON S. BISKIND, Westport, Conn., and GORDON ROSENBLUM, Los Angeles

Wednesday, June 3—9 a. m.

ELECTION OF OFFICERS

Physiological and Clinical Aspects of Conception EDWARD T. TYLER, Los Angeles

Discussion to be opened by A. R. BARBANELL, Los Angeles

Relationships of Endometrial Hyperplasia and Adenocarcinoma of the Fundus

EDMUND R. NOVAK, Baltimore

Discussion to be opened by JAMES A. CORSCADEN, New York

Defibrinogenation Syndrome of Obstetrics: Etiology and Management

C. P. HODGKINSON and R. R. MARGULIS, Detroit

Discussion to be opened by CHARLES SCHNEIDER, Detroit

Psychosomatic Aspects of Obstetrics and Gynecology

WILLIAM S. KROGER, Evanston, Ill.

Discussion to be opened by FLANDERS DUNBAR, New York, and A. J. MANDY, Baltimore

The Obstetrical Forceps: Its Use and Abuse

RAYMOND J. PIERI, Syracuse, N. Y.

Discussion to be opened by JOHN F. FIORINO, Everett, Wash.

Thursday, June 4—9 a. m.

Radiological Estimation of Pelvic Expansion

ARTHUR WEINBERG, Far Rockaway, N. Y.

Discussion to be opened by ALAN GUTTMACHER, New York, and WILLIAM F. MENGERT, Dallas, Texas

Management of the Pregnant Diabetic

EDWARD TOLSTOI, WILLIAM P. GIVEN, and R. GORDON DOUGLAS, New York

Discussion to be opened by EDWARD G. WATERS, Jersey City, N. J.

The Contracted Outlet D. FRANK KALTREIDER, Baltimore

Discussion to be opened by EDWARD H. DENNEN, New York

Prolonged Labor: A Clinical Evaluation

JOHN R. MCCAIN, Atlanta, Ga.; CLARENCE L. ANDERSON, Lakeland, Fla.; WILLIAM M. LESTER, Atlanta, Ga., and JOSEPH W. PILKINGTON, St. Petersburg, Fla.

Discussion to be opened by DUNCAN REID, Boston, and LOUIS M. HELLMAN, New York

Elective Appendectomies at the Time of Caesarean Sections

ELISABETH LARSSON, Los Angeles

Discussion to be opened by NICHOLSON J. EASTMAN, Baltimore

CORRECTION

In the article by Dr. George T. Pack and his associates on "Regional Distribution of Moles and Melanomas" published in the December, 1952, issue, page 862, the parenthetical statement at the end of the first footnote in Table 2 should read "From monograph in preparation by Robert Booher and George Pack."

In the article by Dr. Harold I. Miller entitled "Sternum-Splitting Incision for Upper Abdominal Surgery," published in the December 1952 issue, it should have been stated that Dr. Miller assisted Dr. D. Armstrong in Case 3.

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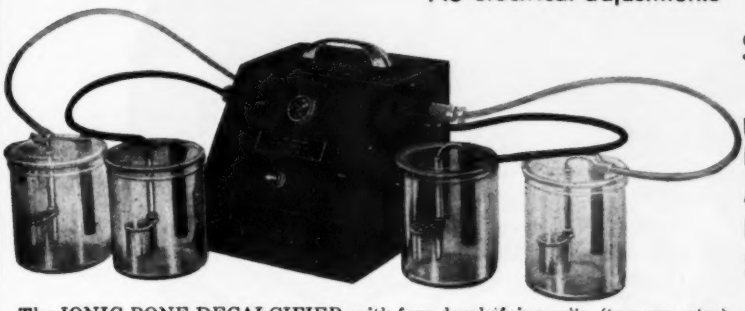

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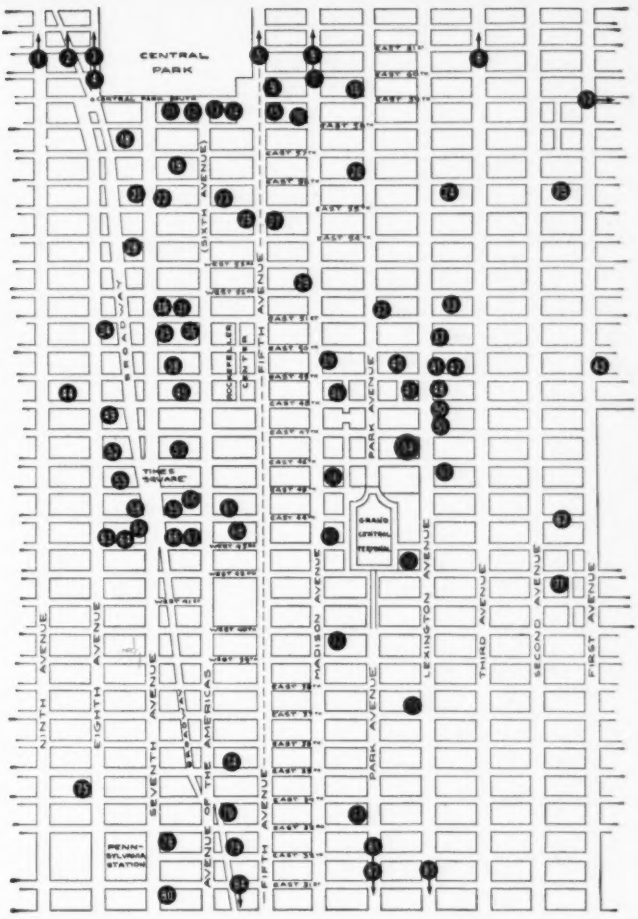

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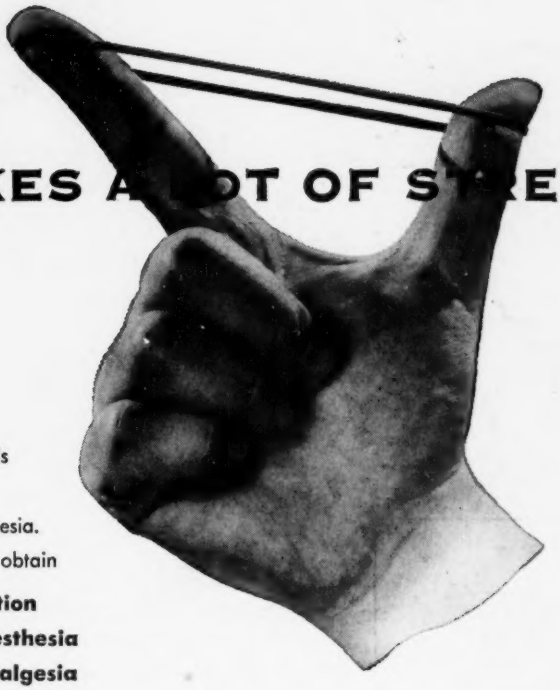

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